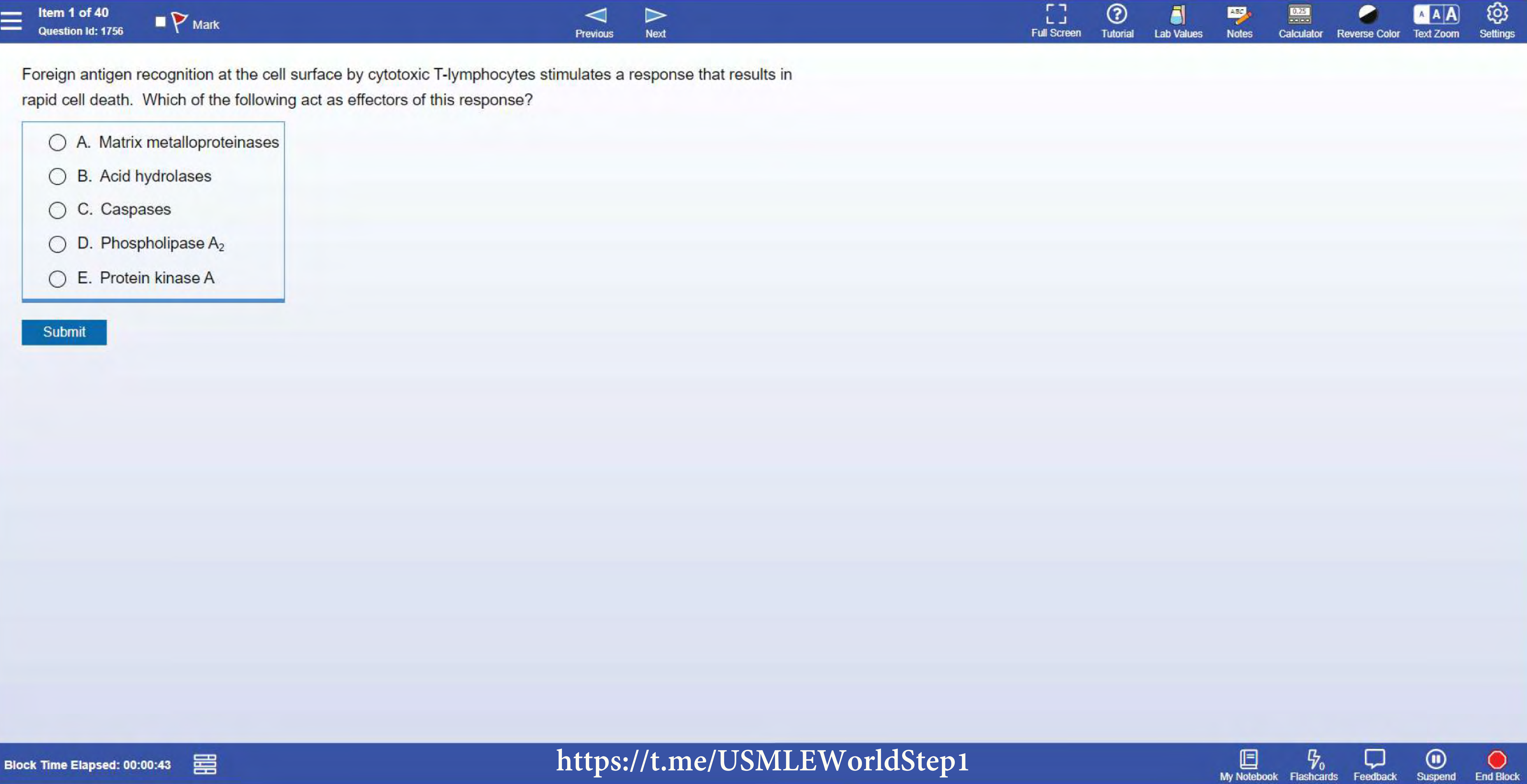
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 1 of 40
Question Id: 1756

Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

○ A. Matrix metalloproteinases
○ B. Acid hydrolases
○ C. Caspases
○ D. Phospholipase A_2
○ E. Protein kinase A

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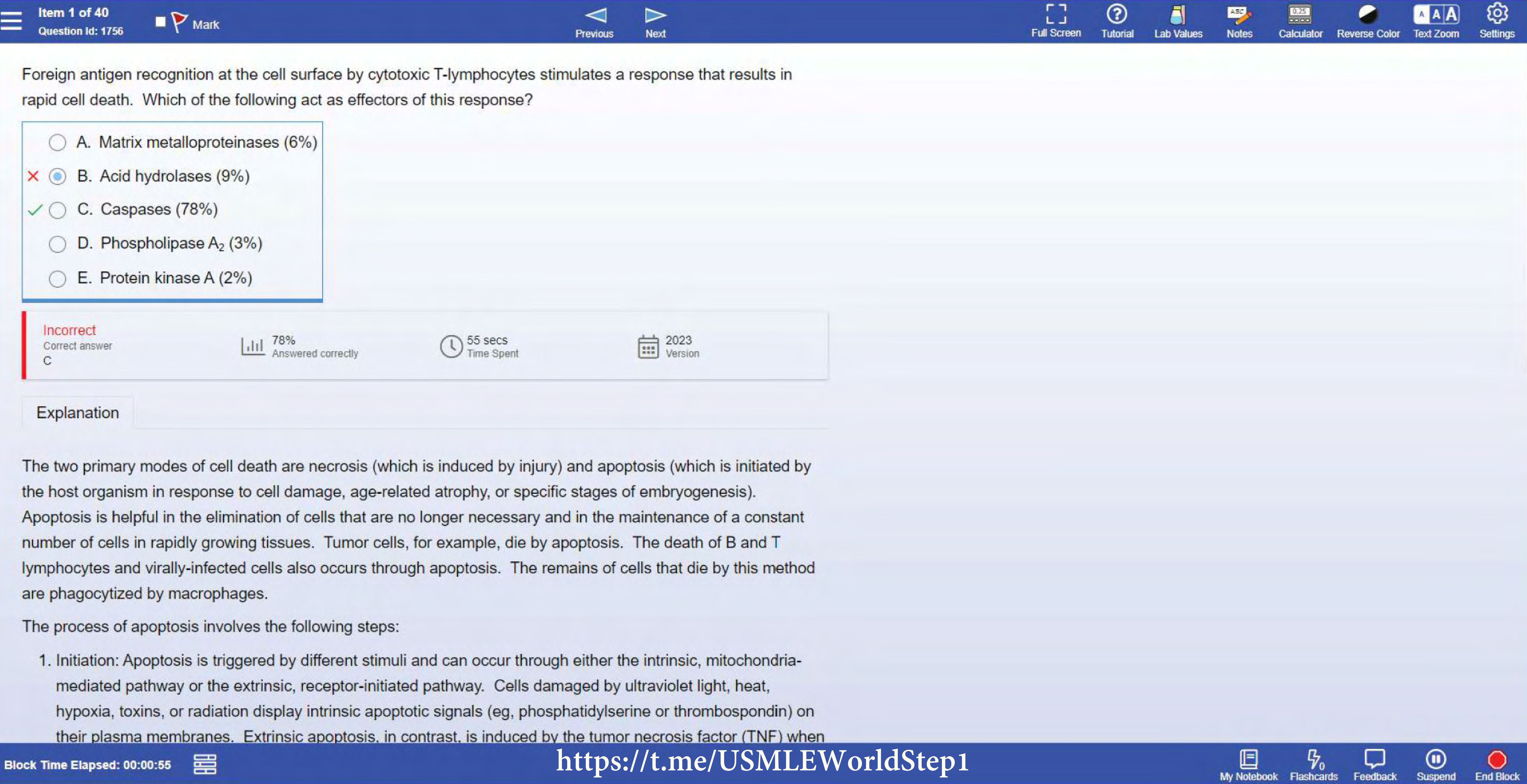
Item 1 of 40
Question Id: 1756
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

○ A. Matrix metalloproteinases (6%)

✗ ● B. Acid hydrolases (9%)

✓ ○ C. Caspases (78%)

○ D. Phospholipase A_2 (3%)

○ E. Protein kinase A (2%)

Incorrect
Correct answer
C

78%
Answered correctly

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Time Spent

2023
Version

Explanation

The two primary modes of cell death are necrosis (which is induced by injury) and apoptosis (which is initiated by the host organism in response to cell damage, age-related atrophy, or specific stages of embryogenesis). Apoptosis is helpful in the elimination of cells that are no longer necessary and in the maintenance of a constant number of cells in rapidly growing tissues. Tumor cells, for example, die by apoptosis. The death of B and T lymphocytes and virally-infected cells also occurs through apoptosis. The remains of cells that die by this method are phagocytized by macrophages.

The process of apoptosis involves the following steps:

1. Initiation: Apoptosis is triggered by different stimuli and can occur through either the intrinsic, mitochondria-mediated pathway or the extrinsic, receptor-initiated pathway. Cells damaged by ultraviolet light, heat, hypoxia, toxins, or radiation display intrinsic apoptotic signals (eg, phosphatidylserine or thrombospondin) on their plasma membranes. Extrinsic apoptosis, in contrast, is induced by the tumor necrosis factor (TNF) when

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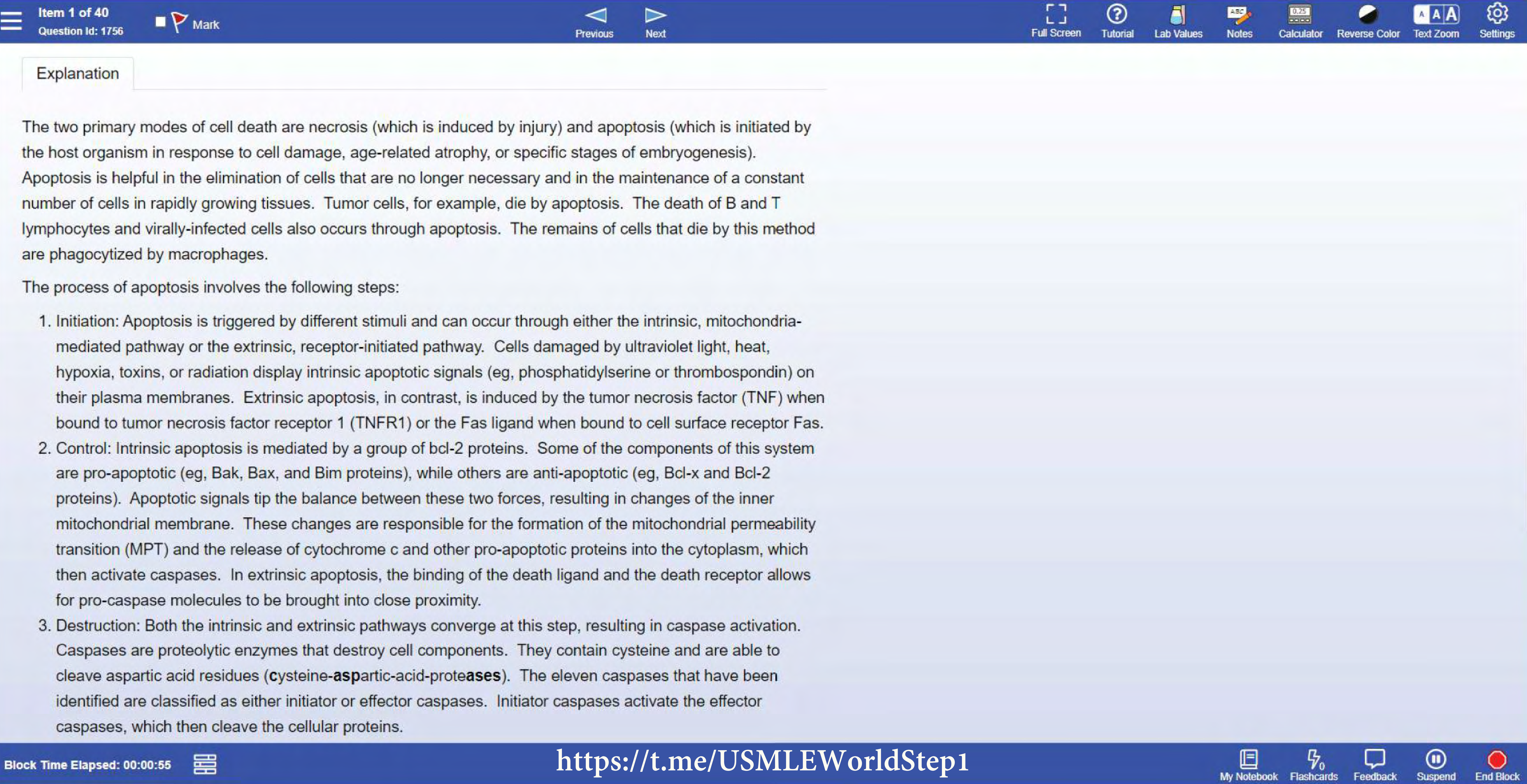
Flashcards
Feedback
Suspend
End Block



The two primary modes of cell death are necrosis (which is induced by injury) and apoptosis (which is initiated by the host organism in response to cell damage, age-related atrophy, or specific stages of embryogenesis). Apoptosis is helpful in the elimination of cells that are no longer necessary and in the maintenance of a constant number of cells in rapidly growing tissues. Tumor cells, for example, die by apoptosis. The death of B and T lymphocytes and virally-infected cells also occurs through apoptosis. The remains of cells that die by this method are phagocytized by macrophages.

The process of apoptosis involves the following steps:

1. Initiation: Apoptosis is triggered by different stimuli and can occur through either the intrinsic, mitochondria-mediated pathway or the extrinsic, receptor-initiated pathway. Cells damaged by ultraviolet light, heat, hypoxia, toxins, or radiation display intrinsic apoptotic signals (eg, phosphatidylserine or thrombospondin) on their plasma membranes. Extrinsic apoptosis, in contrast, is induced by the tumor necrosis factor (TNF) when bound to tumor necrosis factor receptor 1 (TNFR1) or the Fas ligand when bound to cell surface receptor Fas.
2. Control: Intrinsic apoptosis is mediated by a group of bcl-2 proteins. Some of the components of this system are pro-apoptotic (eg, Bak, Bax, and Bim proteins), while others are anti-apoptotic (eg, Bcl-x and Bcl-2 proteins). Apoptotic signals tip the balance between these two forces, resulting in changes of the inner mitochondrial membrane. These changes are responsible for the formation of the mitochondrial permeability transition (MPT) and the release of cytochrome c and other pro-apoptotic proteins into the cytoplasm, which then activate caspases. In extrinsic apoptosis, the binding of the death ligand and the death receptor allows for pro-caspase molecules to be brought into close proximity.
3. Destruction: Both the intrinsic and extrinsic pathways converge at this step, resulting in caspase activation. Caspases are proteolytic enzymes that destroy cell components. They contain cysteine and are able to cleave aspartic acid residues (**c**ysteine-**asp**artic-acid-prote**ases**). The eleven caspases that have been identified are classified as either initiator or effector caspases. Initiator caspases activate the effector caspases, which then cleave the cellular proteins.

Item 1 of 40
Question Id: 1756
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choice A) Metalloproteinases are zinc-containing enzymes that degrade the components of the extracellular matrix (eg, collagen, laminin, fibronectin). Metalloproteinases are essential for proper tissue remodeling during wound healing.

(Choice B) Acid hydrolases do not participate in apoptosis.

(Choice D) Phospholipase A_2 does not participate in apoptosis.

(Choice E) Protein kinase A is a component of the cAMP-associated signaling system. The binding of a ligand to a G-protein-linked receptor results in adenylyl cyclase activation and the release of cAMP. Elevated levels of cAMP activate protein kinase A.

Educational Objective:

Apoptosis can occur through either the intrinsic (mitochondria-mediated) pathway or the extrinsic (receptor-initiated) pathway. Both pathways converge in the activation of caspases. Caspases are proteolytic enzymes that cleave cellular proteins.

Biochemistry	Biochemistry (General Principles)	Cell mediated immunity
Subject	System	Topic

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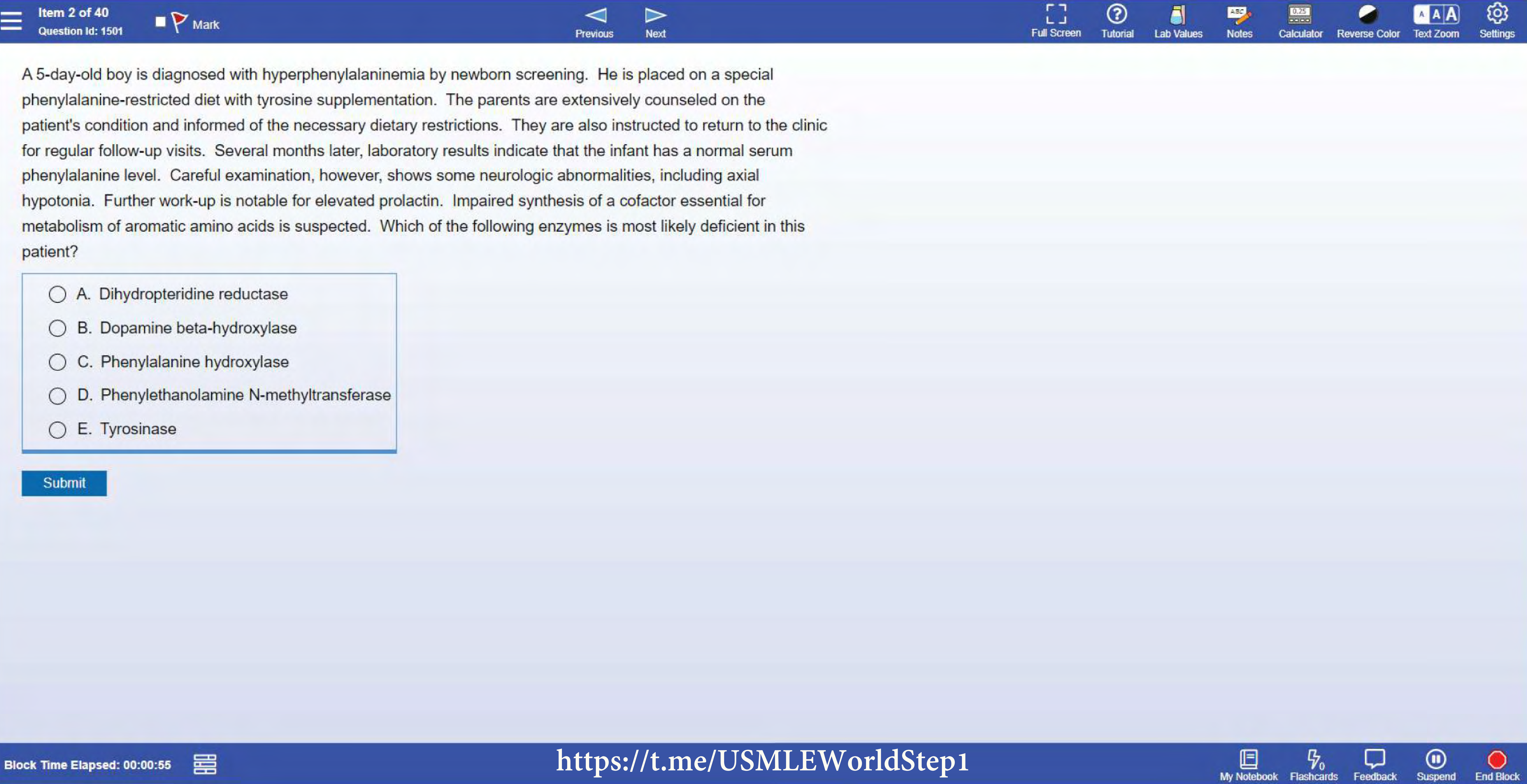

Item 2 of 40
Question Id: 1501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:00:55
My Notebook
Flashcards
Feedback
Suspend
End Block

A 5-day-old boy is diagnosed with hyperphenylalaninemia by newborn screening. He is placed on a special phenylalanine-restricted diet with tyrosine supplementation. The parents are extensively counseled on the patient's condition and informed of the necessary dietary restrictions. They are also instructed to return to the clinic for regular follow-up visits. Several months later, laboratory results indicate that the infant has a normal serum phenylalanine level. Careful examination, however, shows some neurologic abnormalities, including axial hypotonia. Further work-up is notable for elevated prolactin. Impaired synthesis of a cofactor essential for metabolism of aromatic amino acids is suspected. Which of the following enzymes is most likely deficient in this patient?

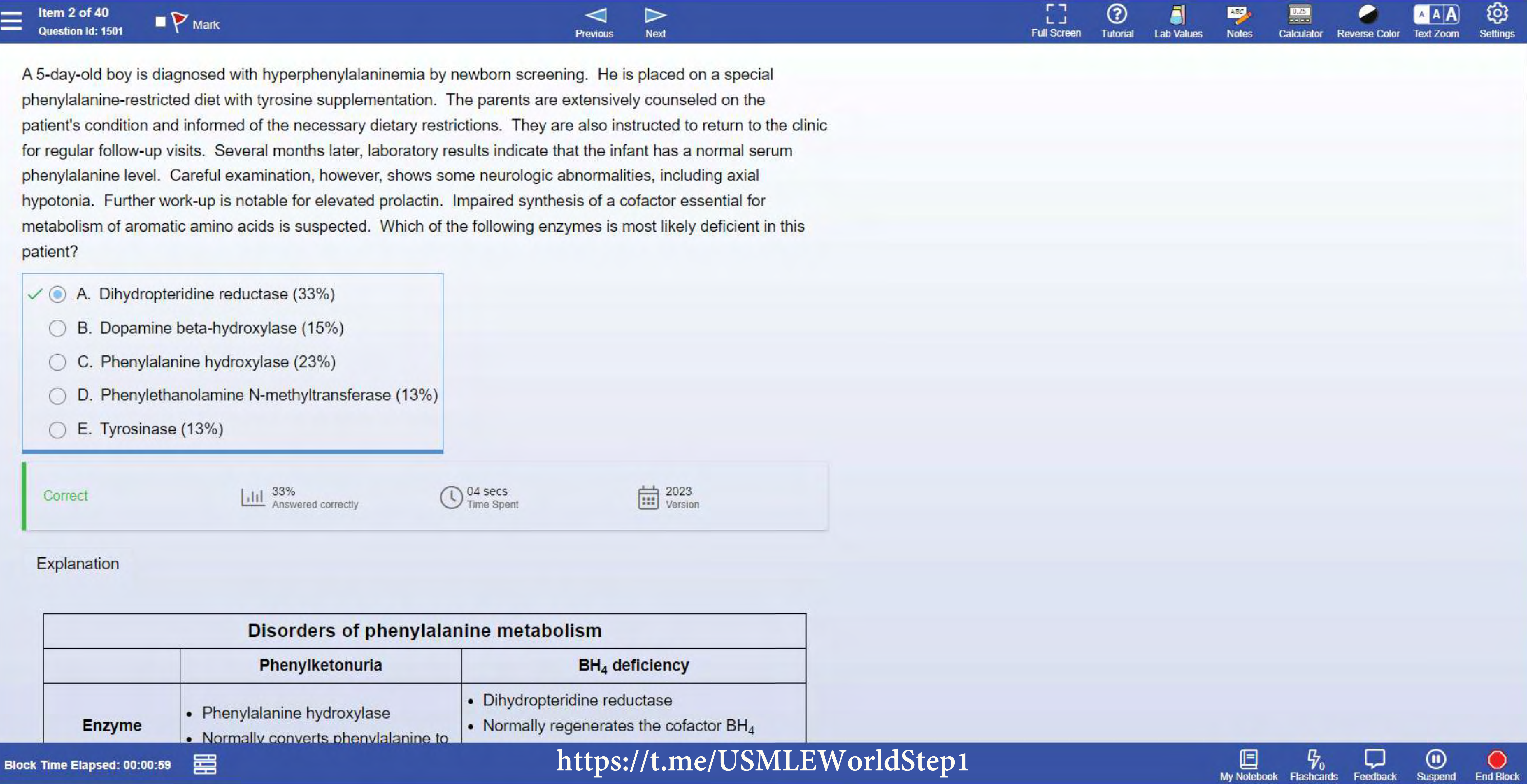
○ A. Dihydropteridine reductase

○ B. Dopamine beta-hydroxylase

○ C. Phenylalanine hydroxylase

○ D. Phenylethanolamine N-methyltransferase

○ E. Tyrosinase


Item 2 of 40
Question Id: 1501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
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✓ ● A. Dihydropteridine reductase (33%)
○ B. Dopamine beta-hydroxylase (15%)
○ C. Phenylalanine hydroxylase (23%)
○ D. Phenylethanolamine N-methyltransferase (13%)
○ E. Tyrosinase (13%)

Correct

33% Answered correctly

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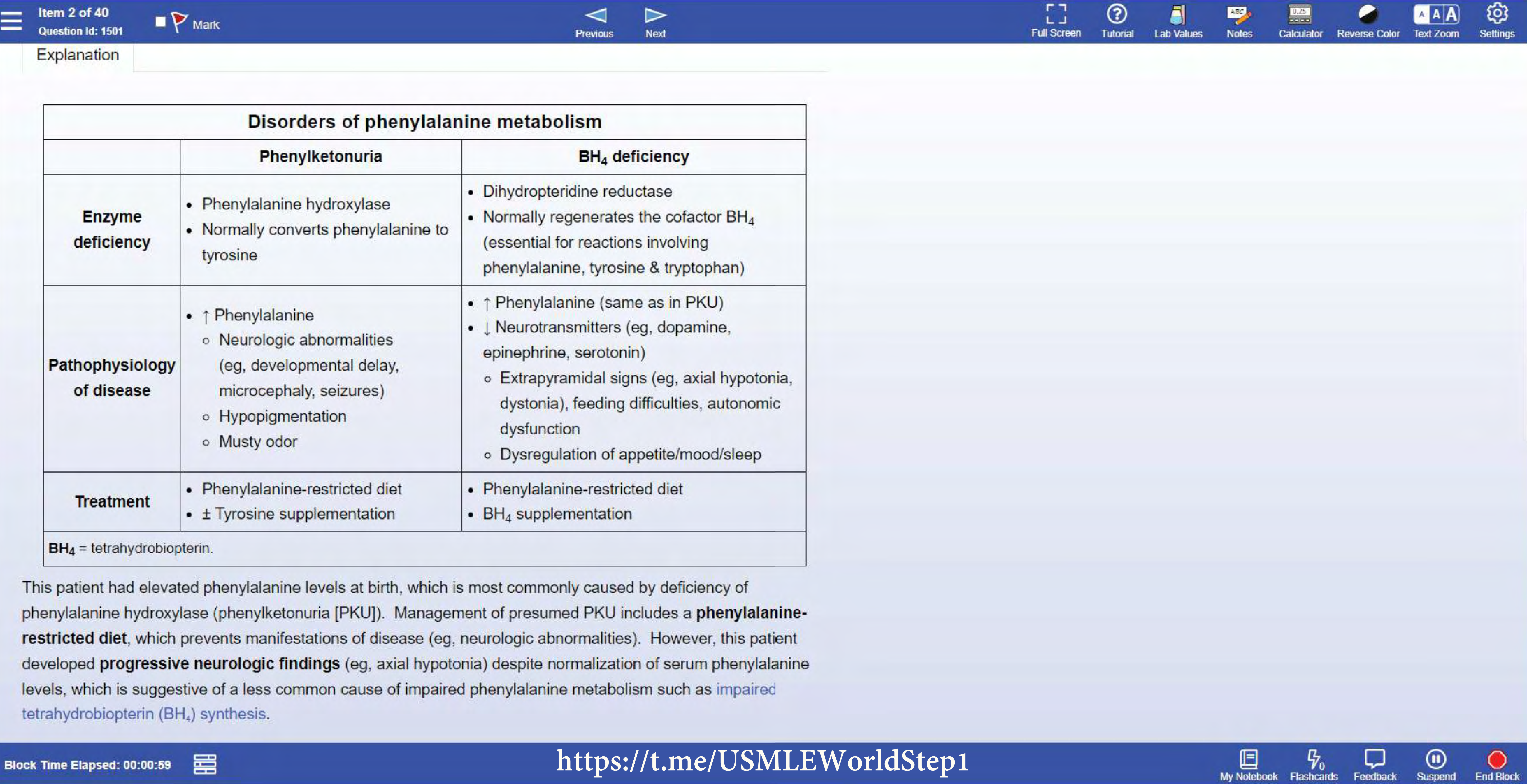
2023 Version

Explanation

Disorders of phenylalanine metabolism

	Phenylketonuria	BH_4 deficiency
Enzyme	Phenylalanine hydroxylase Normally converts phenylalanine to	Dihydropteridine reductase Normally regenerates the cofactor BH_4


Item 2 of 40
Question Id: 1501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Disorders of phenylalanine metabolism		
	Phenylketonuria	**BH$_4$ deficiency**
Enzyme deficiency	• Phenylalanine hydroxylase • Normally converts phenylalanine to tyrosine	• Dihydropteridine reductase • Normally regenerates the cofactor BH$_4$ (essential for reactions involving phenylalanine, tyrosine & tryptophan)
Pathophysiology of disease	• ↑ Phenylalanine ○ Neurologic abnormalities (eg, developmental delay, microcephaly, seizures) ○ Hypopigmentation ○ Musty odor	• ↑ Phenylalanine (same as in PKU) • ↓ Neurotransmitters (eg, dopamine, epinephrine, serotonin) ○ Extrapyramidal signs (eg, axial hypotonia, dystonia), feeding difficulties, autonomic dysfunction ○ Dysregulation of appetite/mood/sleep
Treatment	• Phenylalanine-restricted diet • ± Tyrosine supplementation	• Phenylalanine-restricted diet • BH$_4$ supplementation

BH$_4$ = tetrahydrobiopterin.

This patient had elevated phenylalanine levels at birth, which is most commonly caused by deficiency of phenylalanine hydroxylase (phenylketonuria [PKU]). Management of presumed PKU includes a **phenylalanine-restricted diet**, which prevents manifestations of disease (eg, neurologic abnormalities). However, this patient developed **progressive neurologic findings** (eg, axial hypotonia) despite normalization of serum phenylalanine levels, which is suggestive of a less common cause of impaired phenylalanine metabolism such as impaired tetrahydrobiopterin (BH$_4$) synthesis.

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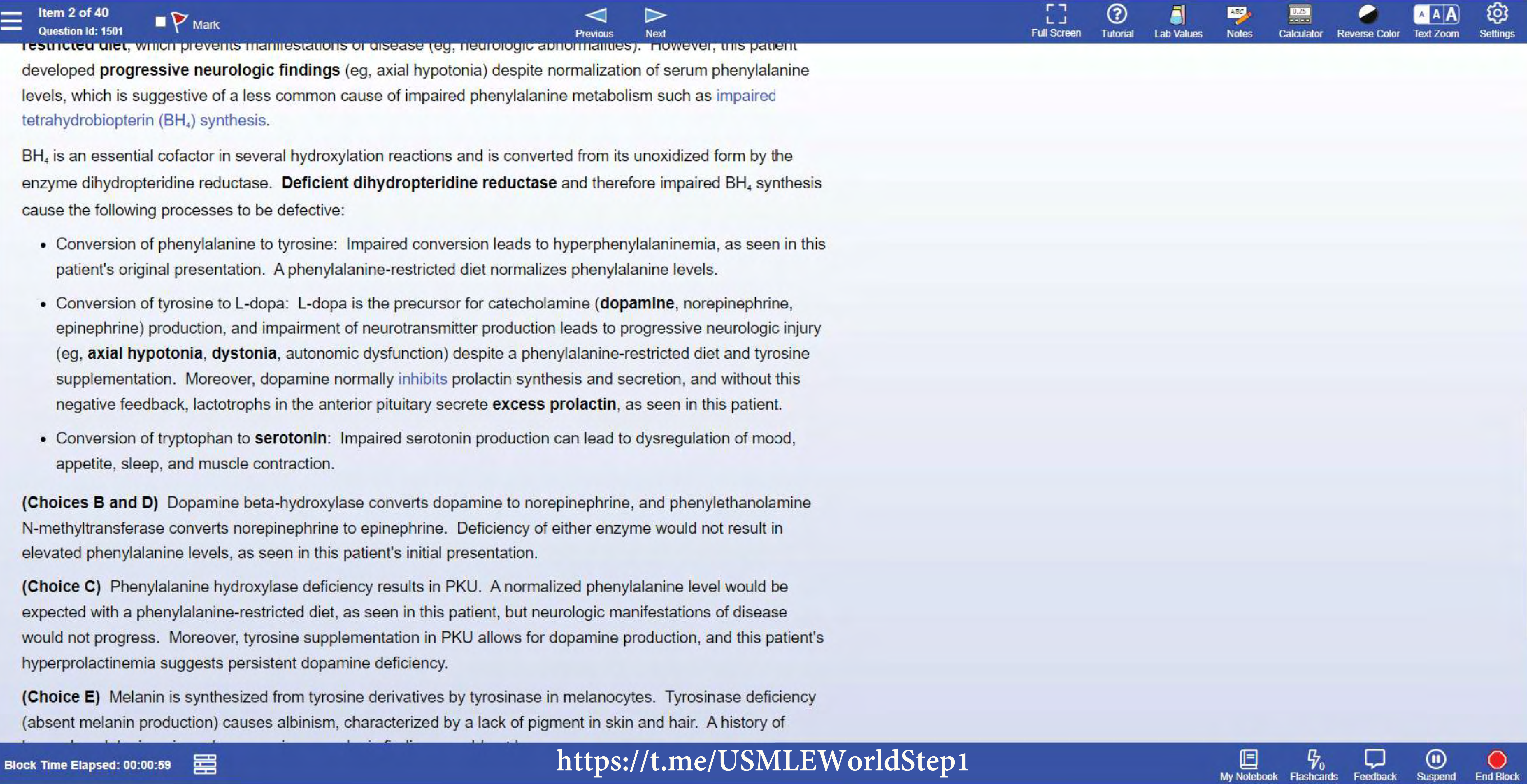
My Notebook
Flashcards
Feedback
Suspend
End Block



restricted diet, which prevents manifestations of disease (eg, neurologic abnormalities). However, this patient developed **progressive neurologic findings** (eg, axial hypotonia) despite normalization of serum phenylalanine levels, which is suggestive of a less common cause of impaired phenylalanine metabolism such as impaired tetrahydrobiopterin (BH_4) synthesis.

BH_4 is an essential cofactor in several hydroxylation reactions and is converted from its unoxidized form by the enzyme dihydropteridine reductase. **Deficient dihydropteridine reductase** and therefore impaired BH_4 synthesis cause the following processes to be defective:

- Conversion of phenylalanine to tyrosine: Impaired conversion leads to hyperphenylalaninemia, as seen in this patient's original presentation. A phenylalanine-restricted diet normalizes phenylalanine levels.
- Conversion of tyrosine to L-dopa: L-dopa is the precursor for catecholamine (**dopamine**, norepinephrine, epinephrine) production, and impairment of neurotransmitter production leads to progressive neurologic injury (eg, **axial hypotonia**, **dystonia**, autonomic dysfunction) despite a phenylalanine-restricted diet and tyrosine supplementation. Moreover, dopamine normally inhibits prolactin synthesis and secretion, and without this negative feedback, lactotrophs in the anterior pituitary secrete **excess prolactin**, as seen in this patient.
- Conversion of tryptophan to **serotonin**: Impaired serotonin production can lead to dysregulation of mood, appetite, sleep, and muscle contraction.

(Choices B and D) Dopamine beta-hydroxylase converts dopamine to norepinephrine, and phenylethanolamine N-methyltransferase converts norepinephrine to epinephrine. Deficiency of either enzyme would not result in elevated phenylalanine levels, as seen in this patient's initial presentation.

(Choice C) Phenylalanine hydroxylase deficiency results in PKU. A normalized phenylalanine level would be expected with a phenylalanine-restricted diet, as seen in this patient, but neurologic manifestations of disease would not progress. Moreover, tyrosine supplementation in PKU allows for dopamine production, and this patient's hyperprolactinemia suggests persistent dopamine deficiency.

(Choice E) Melanin is synthesized from tyrosine derivatives by tyrosinase in melanocytes. Tyrosinase deficiency (absent melanin production) causes albinism, characterized by a lack of pigment in skin and hair. A history of

Item 2 of 40
Question Id: 1501
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

(eg, **axial hypotonia**, **dystonia**, autonomic dysfunction) despite a phenylalanine-restricted diet and tyrosine supplementation. Moreover, dopamine normally inhibits prolactin synthesis and secretion, and without this negative feedback, lactotrophs in the anterior pituitary secrete **excess prolactin**, as seen in this patient.

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(Choice E) Melanin is synthesized from tyrosine derivatives by tyrosinase in melanocytes. Tyrosinase deficiency (absent melanin production) causes albinism, characterized by a lack of pigment in skin and hair. A history of hyperphenylalaninemia and progressive neurologic findings would not be seen.

Educational objective:

Although hyperphenylalaninemia is most commonly due to phenylketonuria, progressive neurologic injury despite appropriate treatment (phenylalanine-restricted diet, tyrosine supplementation) should raise concern for impaired tetrahydrobiopterin synthesis. This distinct disorder of phenylalanine metabolism is often due to dihydropteridine reductase deficiency, resulting in the inability to synthesize critical neurotransmitters (eg, dopamine, serotonin).

References

- Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain.

Biochemistry	Biochemistry (General Principles)	Phenylketonuria
Subject	System	Topic

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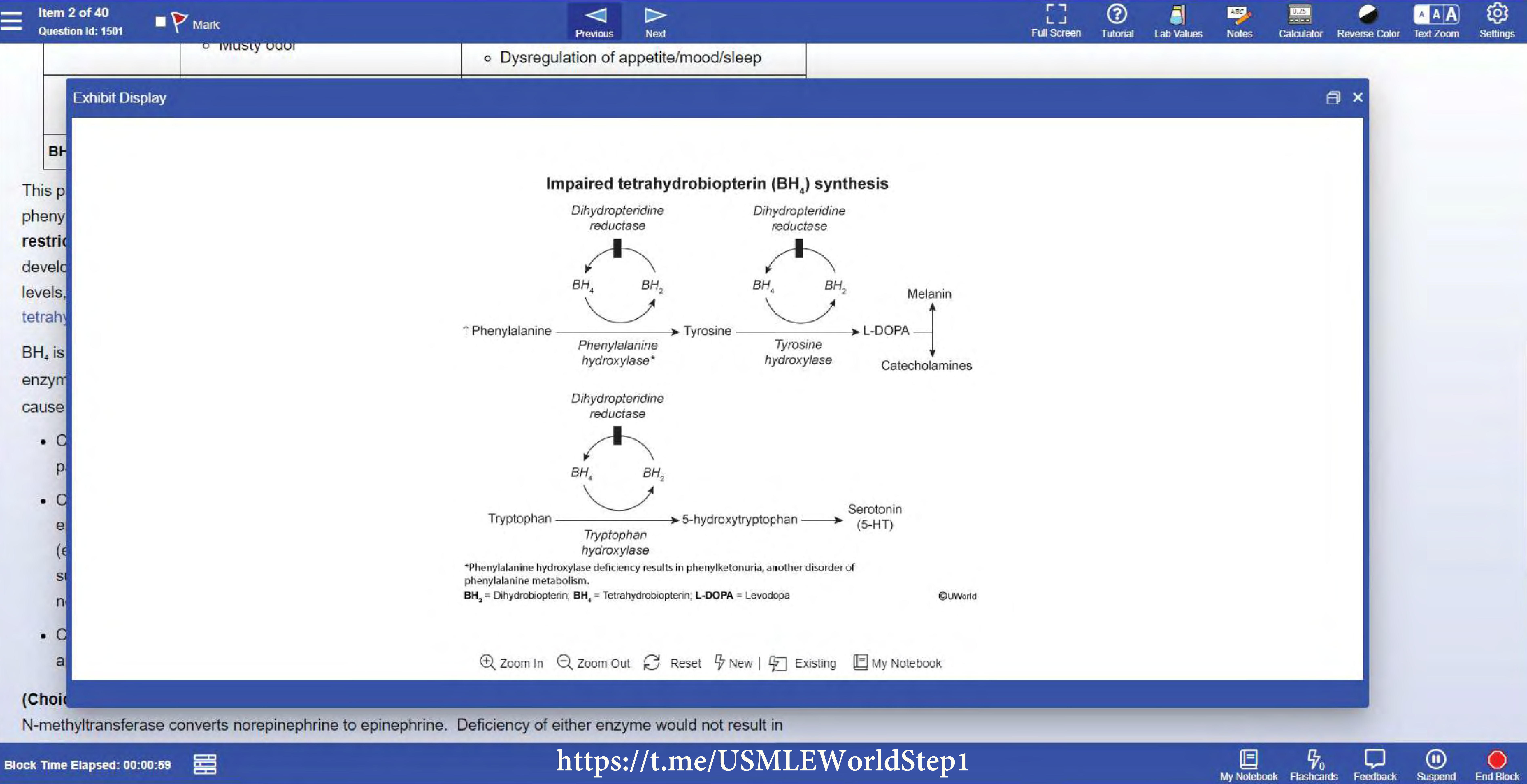
Item 2 of 40
Question Id: 1501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
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BH2
Dihydropteridine reductase
↑ Phenylalanine
Tyrosine
L-DOPA
Melanin
Catecholamines
Phenylalanine hydroxylase*
Tyrosine hydroxylase
Tryptophan
5-hydroxytryptophan
Serotonin (5-HT)
Tryptophan hydroxylase
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My Notebook
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- Dysregulation of appetite/mood/sleep

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Impaired tetrahydrobiopterin (BH_4) synthesis

*Phenylalanine hydroxylase deficiency results in phenylketonuria, another disorder of phenylalanine metabolism.

BH_2 = Dihydrobiopterin; **BH_4** = Tetrahydrobiopterin; **L-DOPA** = Levodopa

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N-methyltransferase converts norepinephrine to epinephrine. Deficiency of either enzyme would not result in

BH_4 = tetrahydrobiopterin.

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expected with a phenylalanine-restricted diet, as seen in this patient, but neurologic manifestations of disease

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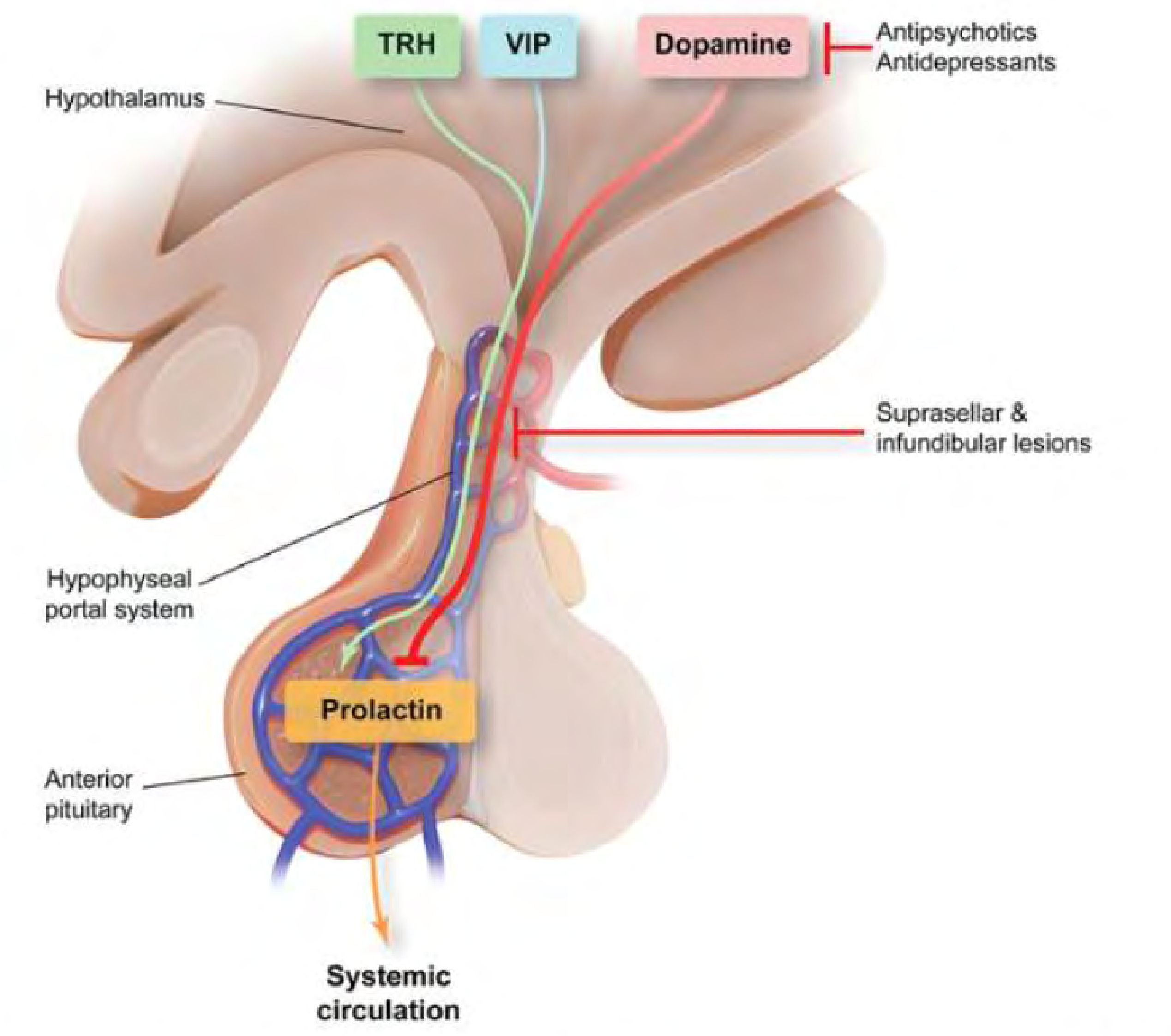
Prolactin


TRH
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Dopamine
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Antidepressants
Hypothalamus
Suprasellar &
infundibular lesions
Hypophyseal
portal system
Prolactin
Anterior
pituitary
Systemic
circulation

TRH = thyrotropin-releasing hormone; **VIP** = vasoactive intestinal peptide.

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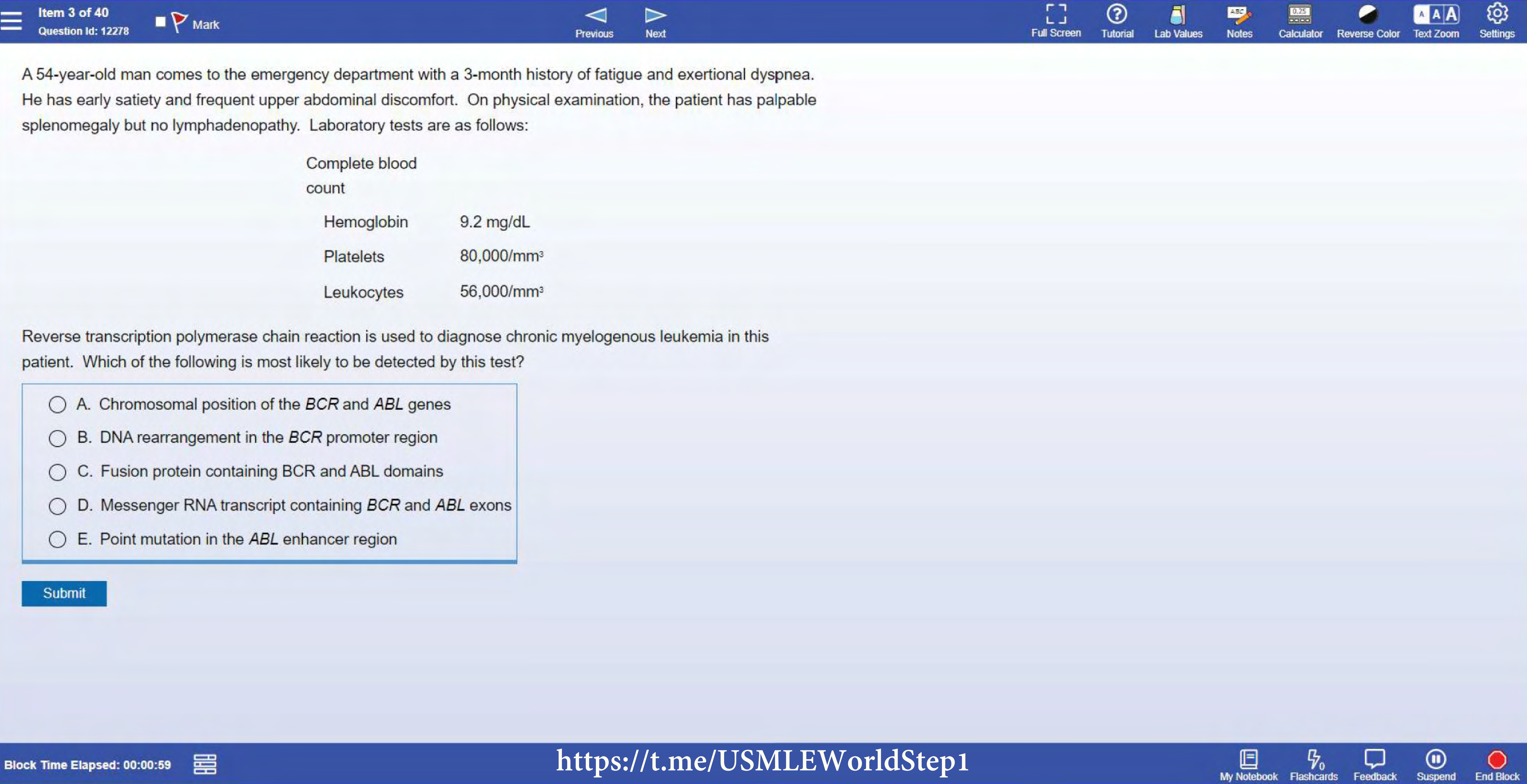

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 3 of 40
Question Id: 12278

A 54-year-old man comes to the emergency department with a 3-month history of fatigue and exertional dyspnea. He has early satiety and frequent upper abdominal discomfort. On physical examination, the patient has palpable splenomegaly but no lymphadenopathy. Laboratory tests are as follows:

Complete blood count	
Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

○ A. Chromosomal position of the *BCR* and *ABL* genes
○ B. DNA rearrangement in the *BCR* promoter region
○ C. Fusion protein containing BCR and ABL domains
○ D. Messenger RNA transcript containing *BCR* and *ABL* exons
○ E. Point mutation in the *ABL* enhancer region

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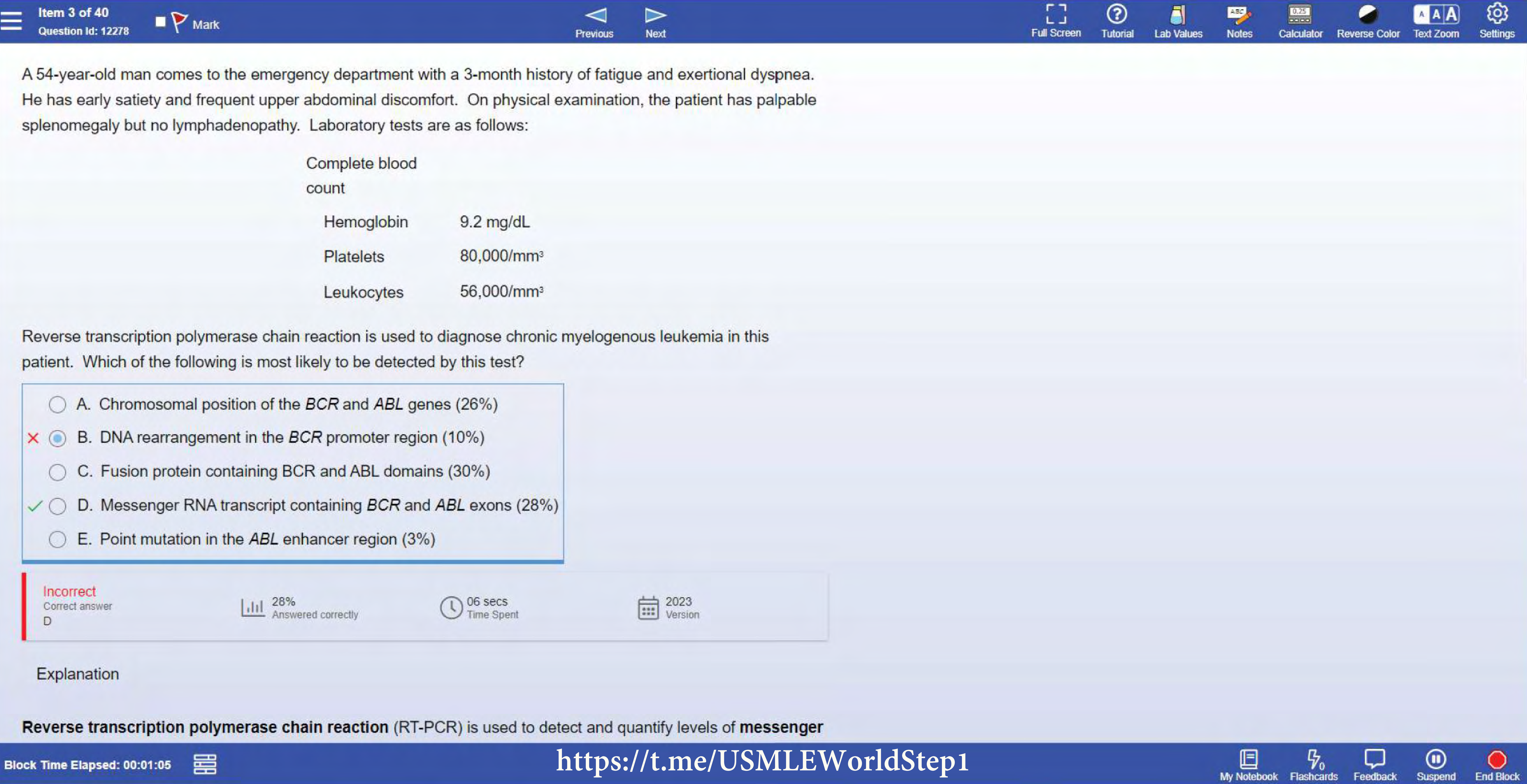
Item 3 of 40
Question Id: 12278
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
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Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

- ○ A. Chromosomal position of the *BCR* and *ABL* genes (26%)
- ✗ ● B. DNA rearrangement in the *BCR* promoter region (10%)
- ○ C. Fusion protein containing BCR and ABL domains (30%)
- ✓ ○ D. Messenger RNA transcript containing *BCR* and *ABL* exons (28%)
- ○ E. Point mutation in the *ABL* enhancer region (3%)

Incorrect
Correct answer
D

28%
Answered correctly

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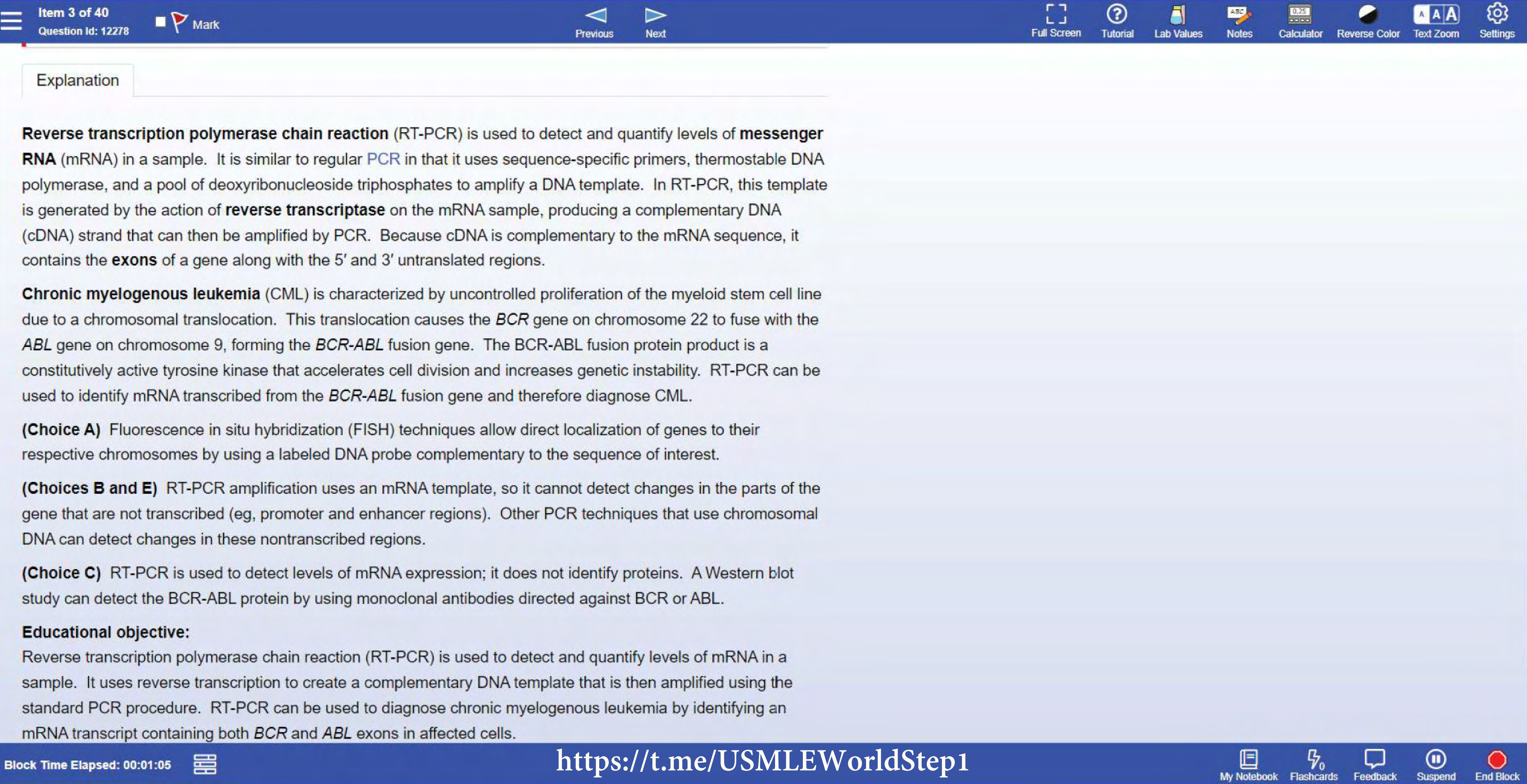
2023
Version

Explanation

Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of **messenger**



Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of **messenger RNA** (mRNA) in a sample. It is similar to regular PCR in that it uses sequence-specific primers, thermostable DNA polymerase, and a pool of deoxyribonucleoside triphosphates to amplify a DNA template. In RT-PCR, this template is generated by the action of **reverse transcriptase** on the mRNA sample, producing a complementary DNA (cDNA) strand that can then be amplified by PCR. Because cDNA is complementary to the mRNA sequence, it contains the **exons** of a gene along with the 5′ and 3′ untranslated regions.

Chronic myelogenous leukemia (CML) is characterized by uncontrolled proliferation of the myeloid stem cell line due to a chromosomal translocation. This translocation causes the *BCR* gene on chromosome 22 to fuse with the *ABL* gene on chromosome 9, forming the *BCR-ABL* fusion gene. The BCR-ABL fusion protein product is a constitutively active tyrosine kinase that accelerates cell division and increases genetic instability. RT-PCR can be used to identify mRNA transcribed from the *BCR-ABL* fusion gene and therefore diagnose CML.

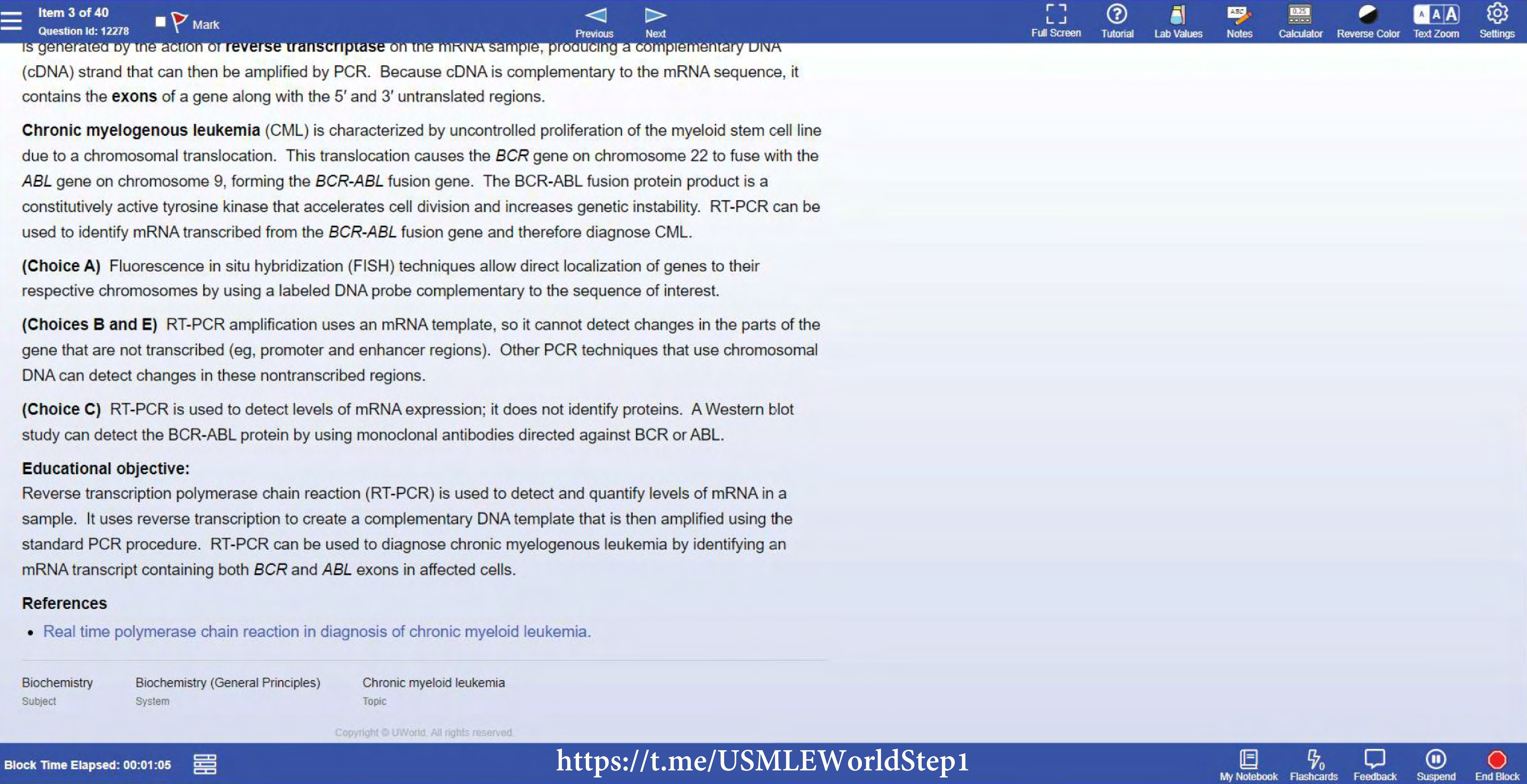
(Choice A) Fluorescence in situ hybridization (FISH) techniques allow direct localization of genes to their respective chromosomes by using a labeled DNA probe complementary to the sequence of interest.

(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the parts of the gene that are not transcribed (eg, promoter and enhancer regions). Other PCR techniques that use chromosomal DNA can detect changes in these nontranscribed regions.

(Choice C) RT-PCR is used to detect levels of mRNA expression; it does not identify proteins. A Western blot study can detect the BCR-ABL protein by using monoclonal antibodies directed against BCR or ABL.

Educational objective:

Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of mRNA in a sample. It uses reverse transcription to create a complementary DNA template that is then amplified using the standard PCR procedure. RT-PCR can be used to diagnose chronic myelogenous leukemia by identifying an mRNA transcript containing both *BCR* and *ABL* exons in affected cells.



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References

- Real time polymerase chain reaction in diagnosis of chronic myeloid leukemia.

Biochemistry	Biochemistry (General Principles)	Chronic myeloid leukemia
Subject	System	Topic

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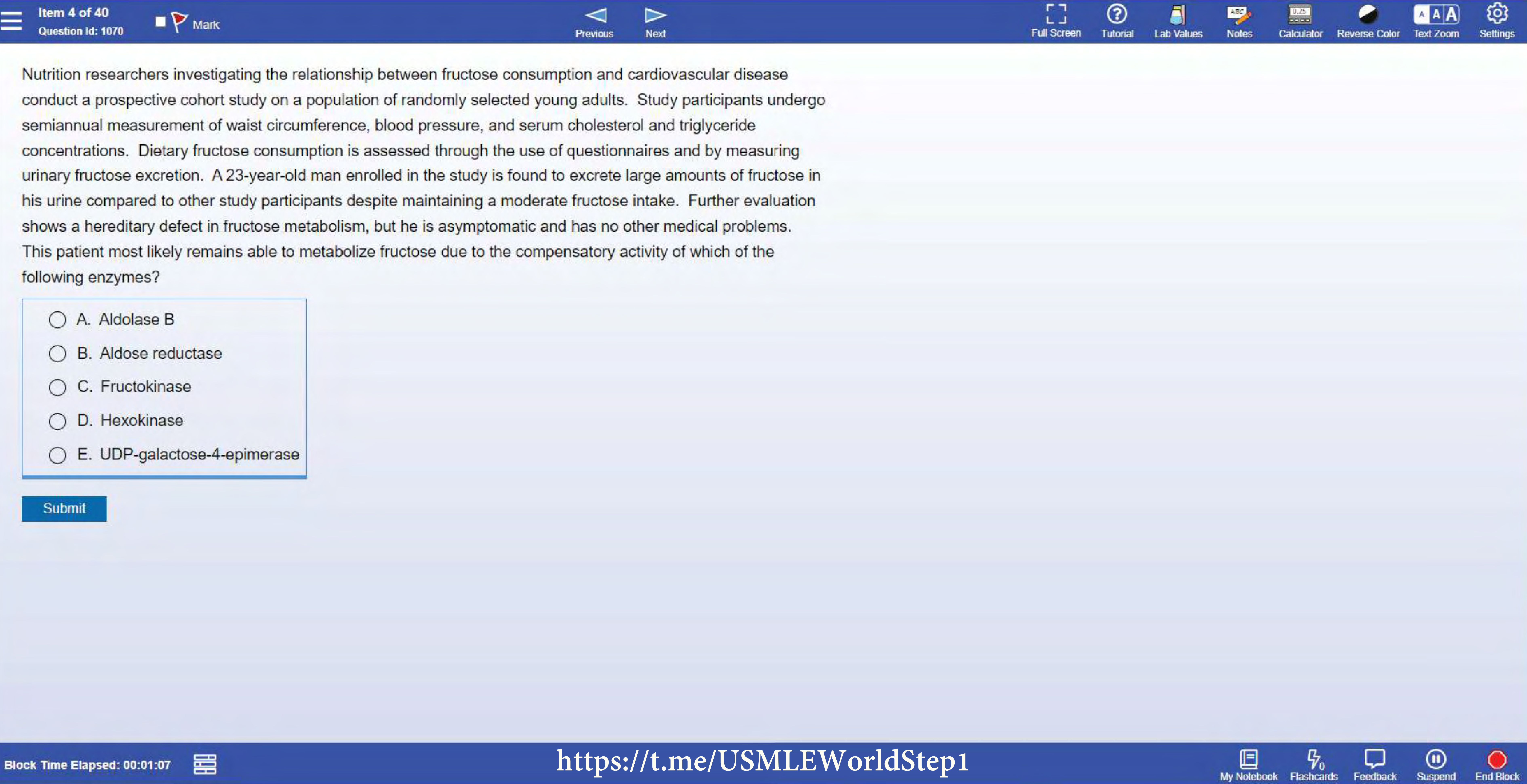
Item 4 of 40
Question Id: 1070
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Nutrition researchers investigating the relationship between fructose consumption and cardiovascular disease conduct a prospective cohort study on a population of randomly selected young adults. Study participants undergo semiannual measurement of waist circumference, blood pressure, and serum cholesterol and triglyceride concentrations. Dietary fructose consumption is assessed through the use of questionnaires and by measuring urinary fructose excretion. A 23-year-old man enrolled in the study is found to excrete large amounts of fructose in his urine compared to other study participants despite maintaining a moderate fructose intake. Further evaluation shows a hereditary defect in fructose metabolism, but he is asymptomatic and has no other medical problems. This patient most likely remains able to metabolize fructose due to the compensatory activity of which of the following enzymes?

○ A. Aldolase B
○ B. Aldose reductase
○ C. Fructokinase
○ D. Hexokinase
○ E. UDP-galactose-4-epimerase

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My Notebook
Flashcards
Feedback
Suspend
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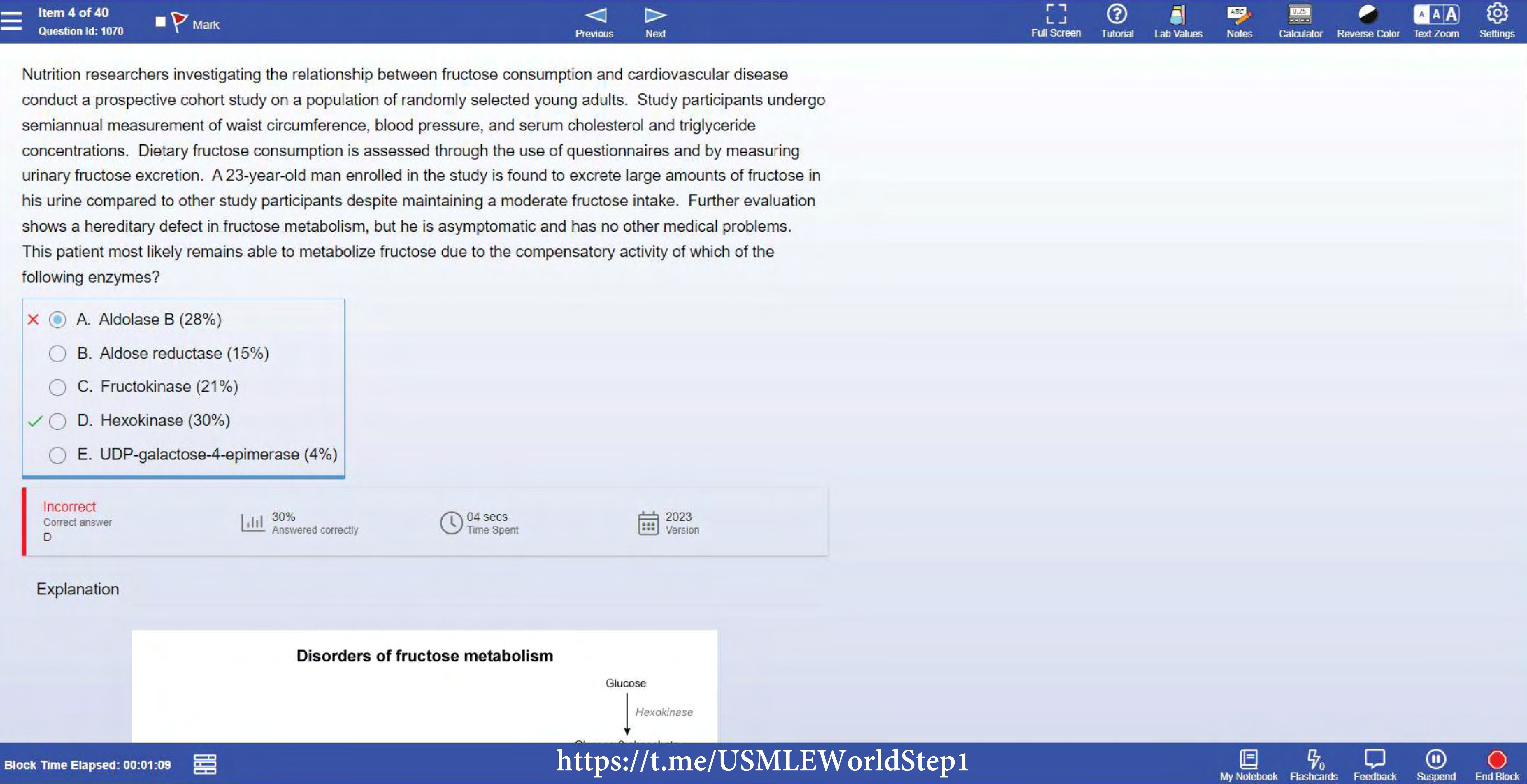
Item 4 of 40
Question Id: 1070
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Nutrition researchers investigating the relationship between fructose consumption and cardiovascular disease conduct a prospective cohort study on a population of randomly selected young adults. Study participants undergo semiannual measurement of waist circumference, blood pressure, and serum cholesterol and triglyceride concentrations. Dietary fructose consumption is assessed through the use of questionnaires and by measuring urinary fructose excretion. A 23-year-old man enrolled in the study is found to excrete large amounts of fructose in his urine compared to other study participants despite maintaining a moderate fructose intake. Further evaluation shows a hereditary defect in fructose metabolism, but he is asymptomatic and has no other medical problems. This patient most likely remains able to metabolize fructose due to the compensatory activity of which of the following enzymes?

✗ ● A. Aldolase B (28%)
○ B. Aldose reductase (15%)
○ C. Fructokinase (21%)
✓ ○ D. Hexokinase (30%)
○ E. UDP-galactose-4-epimerase (4%)

Incorrect
Correct answer
D

30%
Answered correctly

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2023
Version

Explanation

Disorders of fructose metabolism

Glucose
Hexokinase

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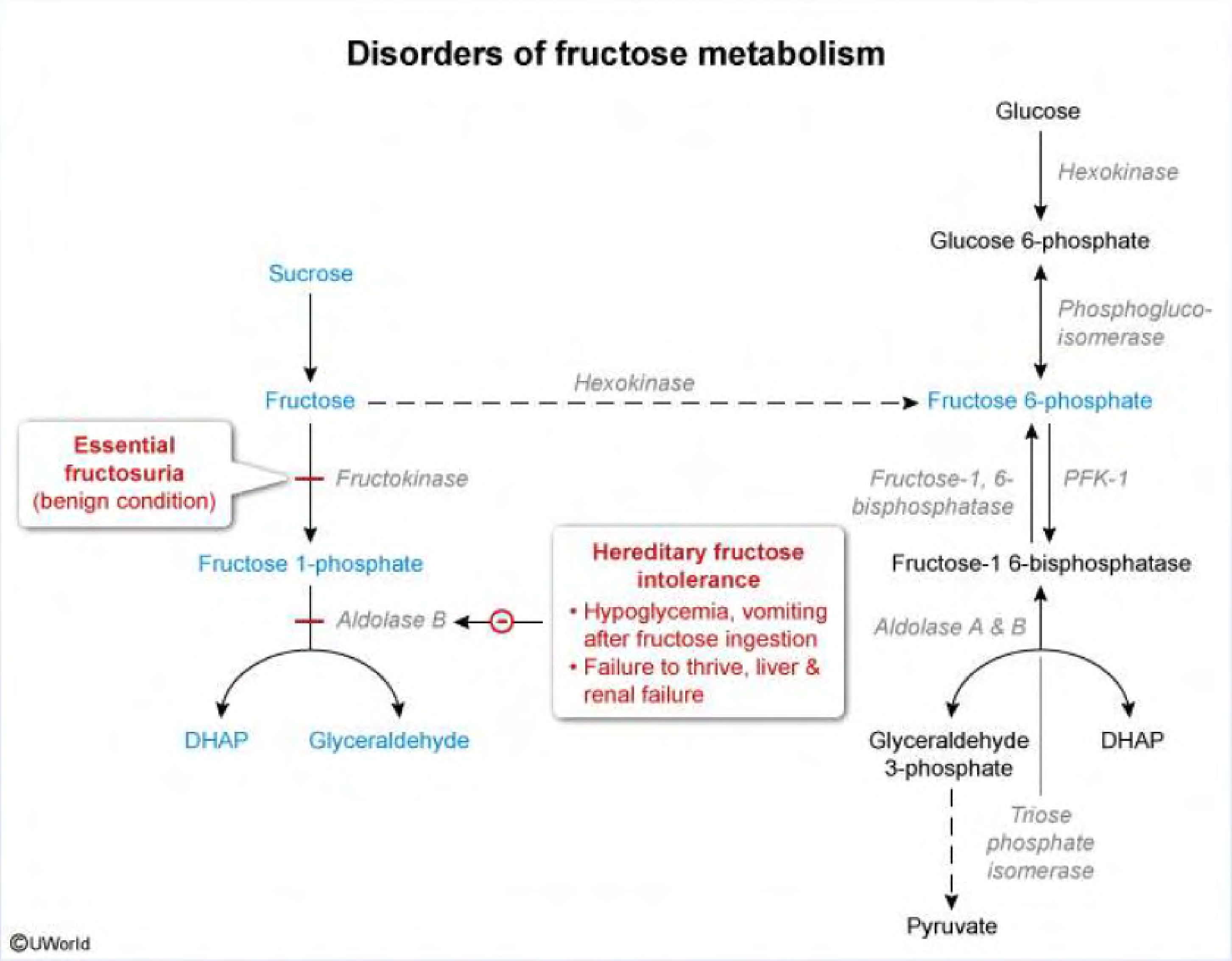
My Notebook
Flashcards
Feedback
Suspend
End Block

Explanation


Disorders of fructose metabolism
Glucose
Hexokinase
Glucose 6-phosphate
Phosphogluco-isomerase
Sucrose
Fructose
Hexokinase
Fructose 6-phosphate
Essential fructosuria (benign condition)
Fructokinase
Fructose-1, 6-bisphosphatase
PFK-1
Fructose 1-phosphate
Hereditary fructose intolerance
• Hypoglycemia, vomiting after fructose ingestion
• Failure to thrive, liver & renal failure
Fructose-1 6-bisphosphatase
Aldolase B
Aldolase A & B
DHAP
Glyceraldehyde
Glyceraldehyde 3-phosphate
DHAP
Triose phosphate isomerase
Pyruvate

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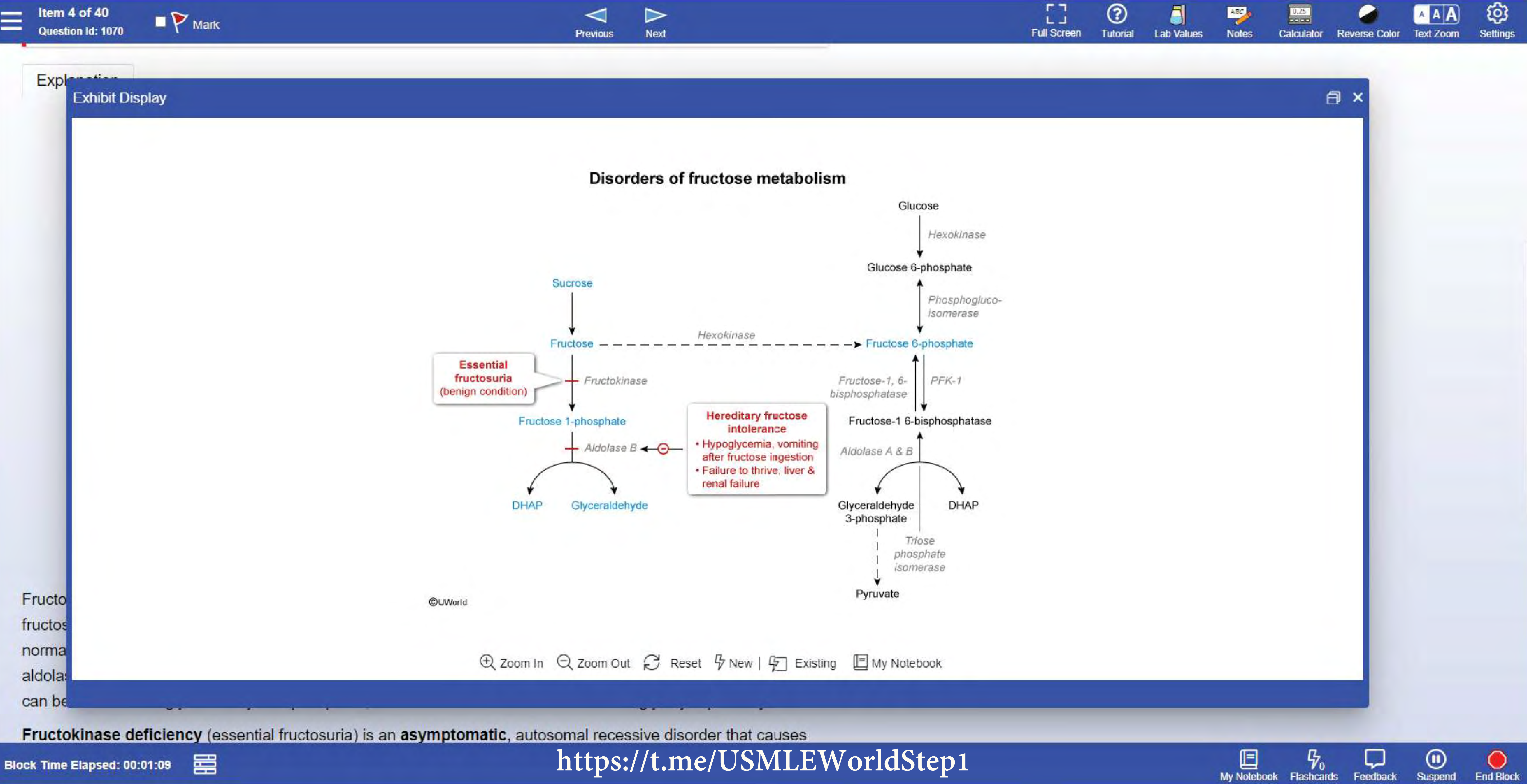
Fructose is obtained in the diet primarily from fruits and food sweeteners such as table sugar (sucrose) and high-fructose corn syrup. Fructose is absorbed in the proximal intestine through the GLUT5 fructose transporter. It is normally phosphorylated by **fructokinase** in the liver, yielding **fructose-1-phosphate**, which is converted by aldolase B to dihydroxyacetone phosphate (DHAP) and glyceraldehyde **(Choice C)**. Glyceraldehyde and DHAP can be converted to glyceraldehyde-3-phosphate, which can then be metabolized in the glycolytic pathway.

Fructokinase deficiency (essential fructosuria) is an **asymptomatic**, autosomal recessive disorder that causes



Item 4 of 40
Question Id: 1070
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Disorders of fructose metabolism
Glucose
Hexokinase
Glucose 6-phosphate
Phosphogluco-isomerase
Sucrose
Fructose
Hexokinase
Fructose 6-phosphate
Essential fructosuria
(benign condition)
Fructokinase
Fructose-1, 6-bisphosphatase
PFK-1
Fructose 1-phosphate
Hereditary fructose intolerance
• Hypoglycemia, vomiting after fructose ingestion
• Failure to thrive, liver & renal failure
Fructose-1 6-bisphosphatase
Aldolase B
Aldolase A & B
DHAP
Glyceraldehyde
Glyceraldehyde 3-phosphate
DHAP
Triose phosphate isomerase
Pyruvate
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Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:01:09
My Notebook
Flashcards
Feedback
Suspend
End Block

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Fructokinase deficiency (essential fructosuria) is an **asymptomatic**, autosomal recessive disorder that causes

Item 4 of 40
Question Id: 1070
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

normally phosphorylated by **fructokinase** in the liver, yielding **fructose-1-phosphate**, which is converted by aldolase B to dihydroxyacetone phosphate (DHAP) and glyceraldehyde **(Choice C)**. Glyceraldehyde and DHAP can be converted to glyceraldehyde-3-phosphate, which can then be metabolized in the glycolytic pathway.

Fructokinase deficiency (essential fructosuria) is an **asymptomatic**, autosomal recessive disorder that causes dietary fructose to be excreted unchanged in the urine. In fructokinase deficiency, **hexokinase** takes over the role of fructose metabolism, converting dietary fructose into **fructose-6-phosphate**. Fructose-6-phosphate can be metabolized in the glycolytic pathway or converted to glucose-6-phosphate or glucose-1-phosphate, which can be used in the pentose phosphate pathway or for glycogen synthesis, respectively.

(Choice A) Aldolase B plays a nonessential role in glycolysis due to the redundant function of aldolase A. However, it is particularly important during fructose metabolism as deficiency of this enzyme leads to toxic accumulation of fructose-1-phosphate (hereditary fructose intolerance). This life-threatening disorder presents in infancy after the introduction of fructose-containing foods.

(Choice B) Aldose reductase is the enzyme that converts glucose to sorbitol. Aldose reductase has a low affinity for glucose, and normally only very small amounts of glucose are metabolized by this enzyme. The amount of glucose metabolized by the aldose reductase pathway increases significantly in diabetes mellitus and contributes to chronic complications such as neuropathy and retinopathy.

(Choice E) UDP-galactose-4-epimerase is involved in the metabolism of galactose; it does not play a role in fructose metabolism.

Educational objective:

Essential fructosuria is a benign disorder of fructose metabolism caused by fructokinase deficiency. In patients with essential fructosuria, some of the dietary fructose load is converted by hexokinase to fructose-6-phosphate, which can then enter glycolysis; this pathway is not significant in normal individuals.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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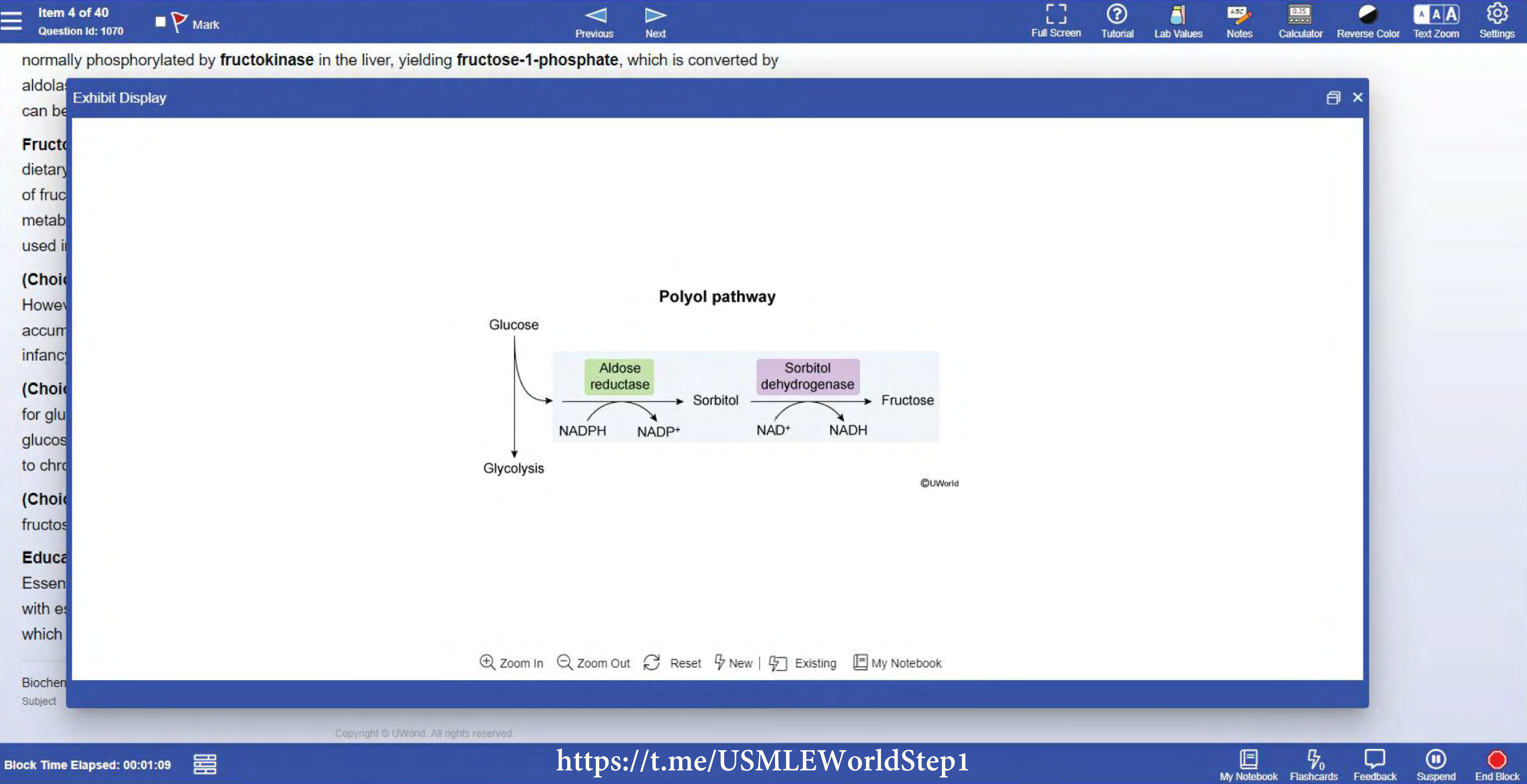

Item 4 of 40
Question Id: 1070
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Polyol pathway

Glucose
Aldose reductase
Sorbitol
Sorbitol dehydrogenase
Fructose
NADPH
NADP⁺
NAD⁺
NADH
Glycolysis

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Zoom Out
Reset
New | Existing
My Notebook

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My Notebook
Flashcards
Feedback
Suspend
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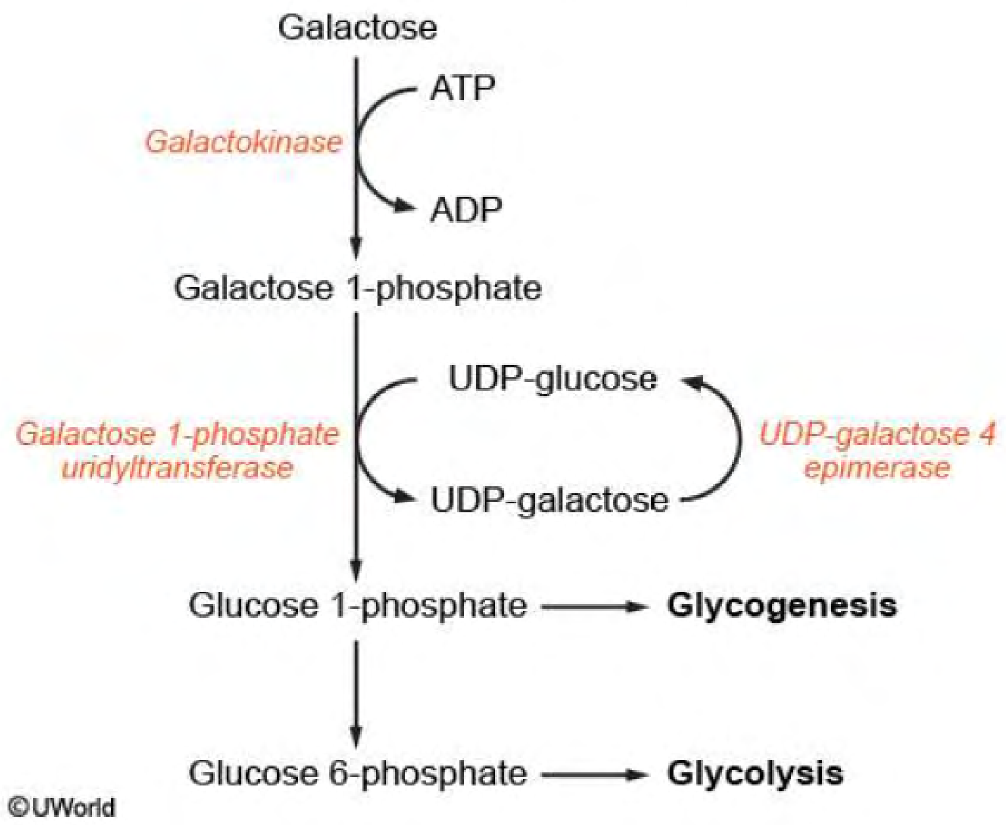
Exhibit Display

Galactose metabolism


Galactose
ATP
Galactokinase
ADP
Galactose 1-phosphate
UDP-glucose
Galactose 1-phosphate uridyltransferase
UDP-galactose 4 epimerase
UDP-galactose
Glucose 1-phosphate
Glycogenesis
Glucose 6-phosphate
Glycolysis
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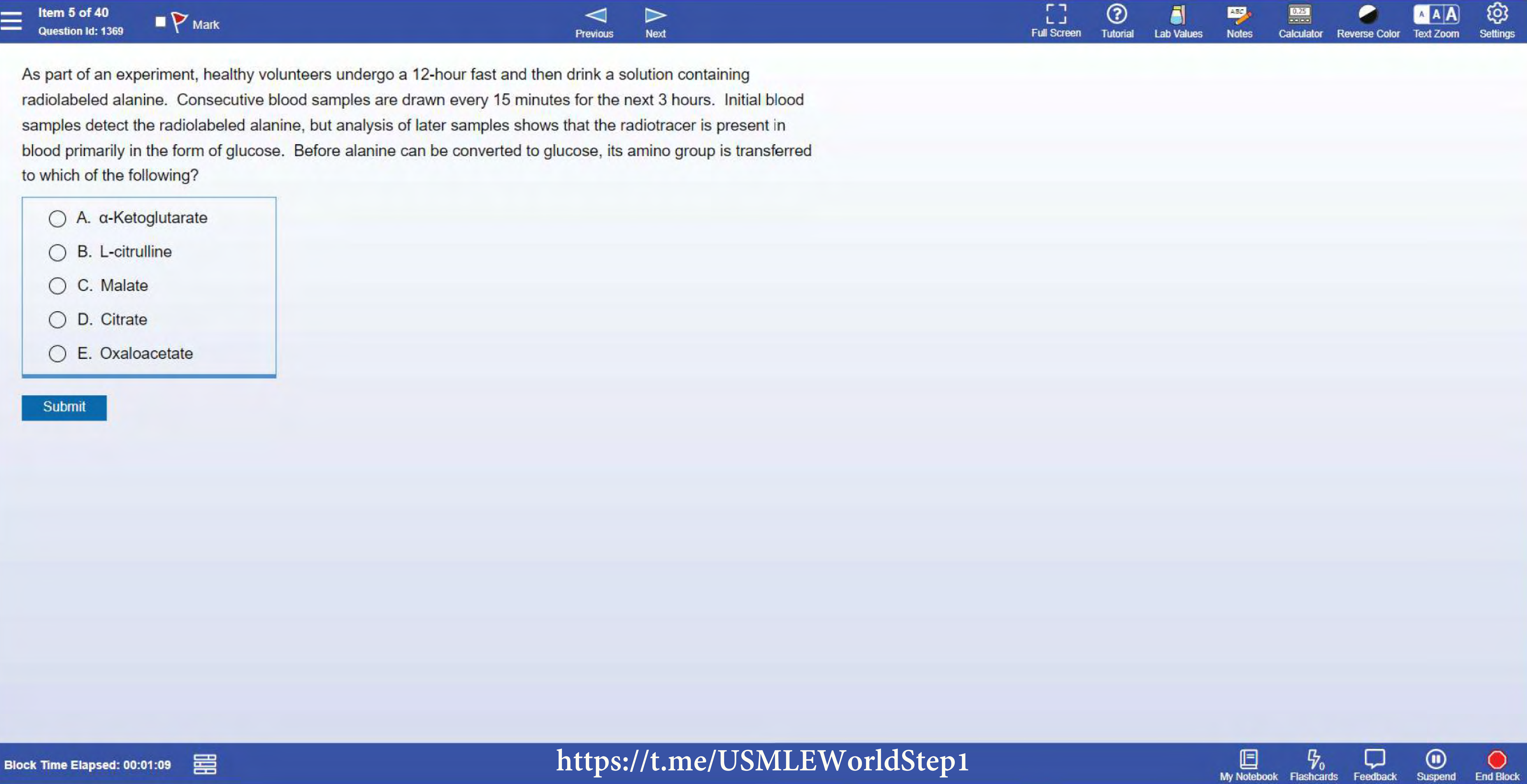
Item 5 of 40
Question Id: 1369
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:01:09
My Notebook
Flashcards
Feedback
Suspend
End Block

As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- ○ A. α-Ketoglutarate
- ○ B. L-citrulline
- ○ C. Malate
- ○ D. Citrate
- ○ E. Oxaloacetate

As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- ✓ ● A. α-Ketoglutarate (61%)
- ○ B. L-citrulline (5%)
- ○ C. Malate (7%)
- ○ D. Citrate (5%)
- ○ E. Oxaloacetate (19%)

Correct

61%
Answered correctly

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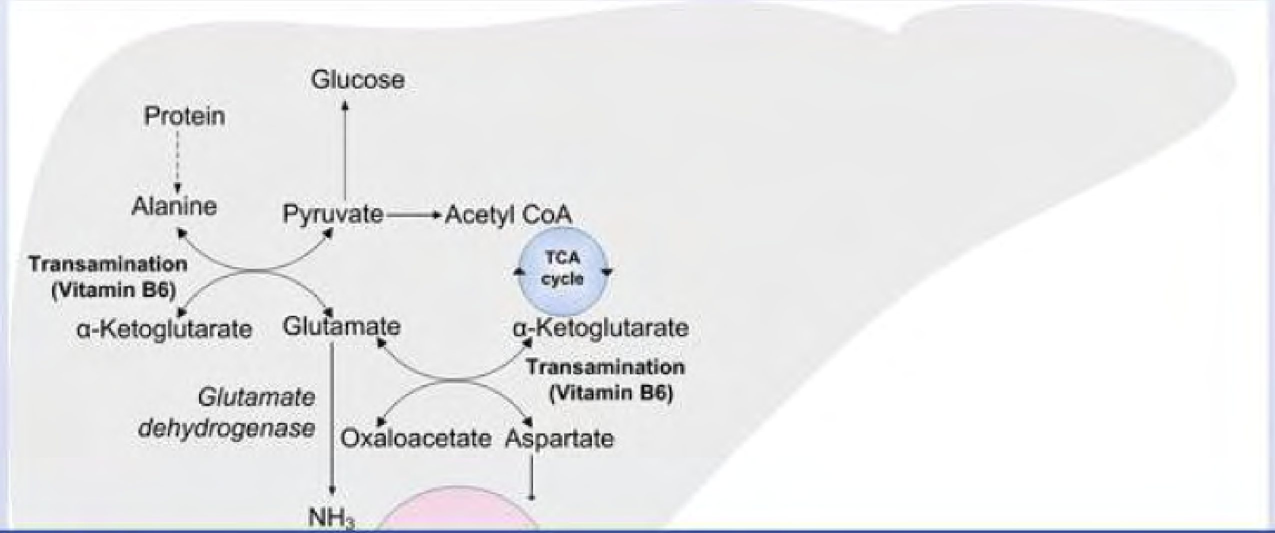
Time Spent

2023
Version

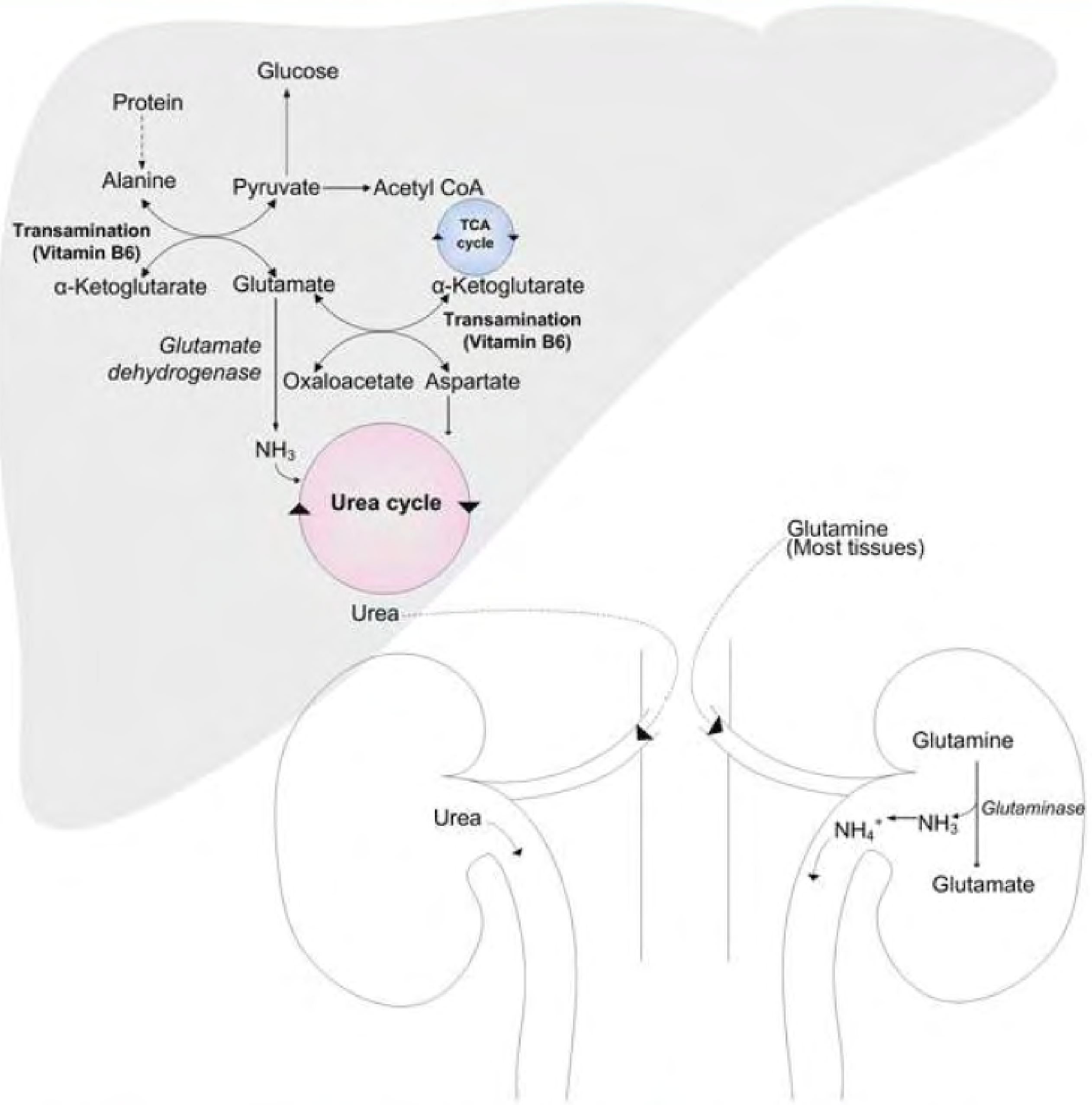
Explanation


Glucose
Protein
Alanine
Pyruvate
Acetyl CoA
TCA cycle
Transamination (Vitamin B6)
α-Ketoglutarate
Glutamate
α-Ketoglutarate
Transamination (Vitamin B6)
Glutamate dehydrogenase
Oxaloacetate
Aspartate
NH₃

Item 5 of 40
Question Id: 1369
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Explanation

Exhibit Display



Glucose
Protein
Alanine
Pyruvate
Acetyl CoA
Transamination (Vitamin B6)
TCA cycle
α-Ketoglutarate
Glutamate
α-Ketoglutarate
Transamination (Vitamin B6)
Glutamate dehydrogenase
Oxaloacetate
Aspartate
NH_3
Urea cycle
Urea
Glutamine (Most tissues)
Glutamine
Glutaminase
NH_4^+
NH_3
Glutamate
Urea

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Alanin

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acid-b

alanine and released into the circulation. Alanine is also released by skeletal muscle tissue during protein catabolism as part of the glucose-alanine cycle that helps remove excess nitrogen. Alanine is then transported to

Block Time Elapsed: 00:01:13

My Notebook
Flashcards
Feedback
Suspend
End Block

Item 5 of 40
Question Id: 1369
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:01:13
My Notebook
Flashcards
Feedback
Suspend
End Block

Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is produced by most body tissues and is catabolized primarily by the gut and kidney for maintenance of cellular metabolism and acid-base regulation, respectively. A significant portion of the glutamine used by these tissues is converted to alanine and released into the circulation. Alanine is also released by skeletal muscle tissue during protein catabolism as part of the glucose-alanine cycle that helps remove excess nitrogen. Alanine is then transported to the liver, where it serves as a vehicle for nitrogen disposal and as a source of carbon skeletons for gluconeogenesis.

In the liver, alanine is transaminated by alanine aminotransferase to pyruvate with the amino group being transferred to α-ketoglutarate to form glutamate. Almost all aminotransferase enzymes use α-ketoglutarate as the amino group acceptor. Thus, amino groups are funneled into glutamate during protein catabolism. Glutamate is further metabolized by the enzyme glutamate dehydrogenase, which liberates free ammonia and regenerates α-ketoglutarate. Ammonia then enters the urea cycle to form urea, the primary disposal form of nitrogen in humans. Urea subsequently enters the blood and is excreted in the urine.

(Choices C, D, and E) Malate, citrate, and oxaloacetate are all intermediates of the tricarboxylic acid cycle.

(Choice B) L-citrulline is an amino acid produced as an intermediate in the conversion of ornithine to argininosuccinate during the hepatic urea cycle.

Educational objective:

Alanine is the major amino acid responsible for transferring nitrogen to the liver for disposal. During the catabolism of proteins, amino groups are transferred to α-ketoglutarate to form glutamate. Glutamate is then processed in the liver to form urea, the primary disposal form of nitrogen in humans. Free ammonia is also excreted into the urine by the kidney for regulation of acid-base status.

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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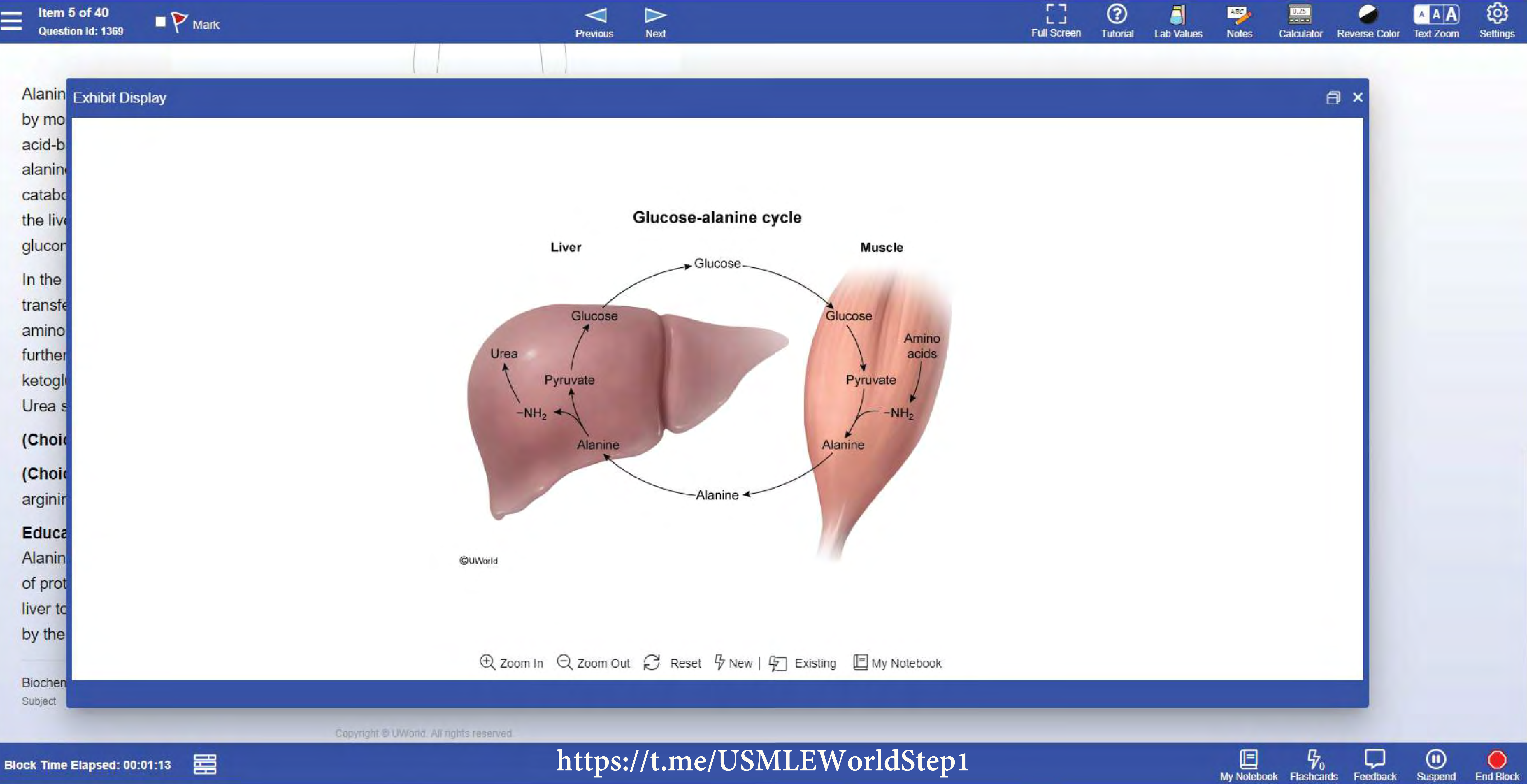
Item 5 of 40
Question Id: 1369
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Glucose-alanine cycle
Liver
Muscle
Glucose
Glucose
Urea
Pyruvate
−NH2
Alanine
Glucose
Amino acids
Pyruvate
−NH2
Alanine
Alanine
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Zoom In
Zoom Out
Reset
New
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My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block

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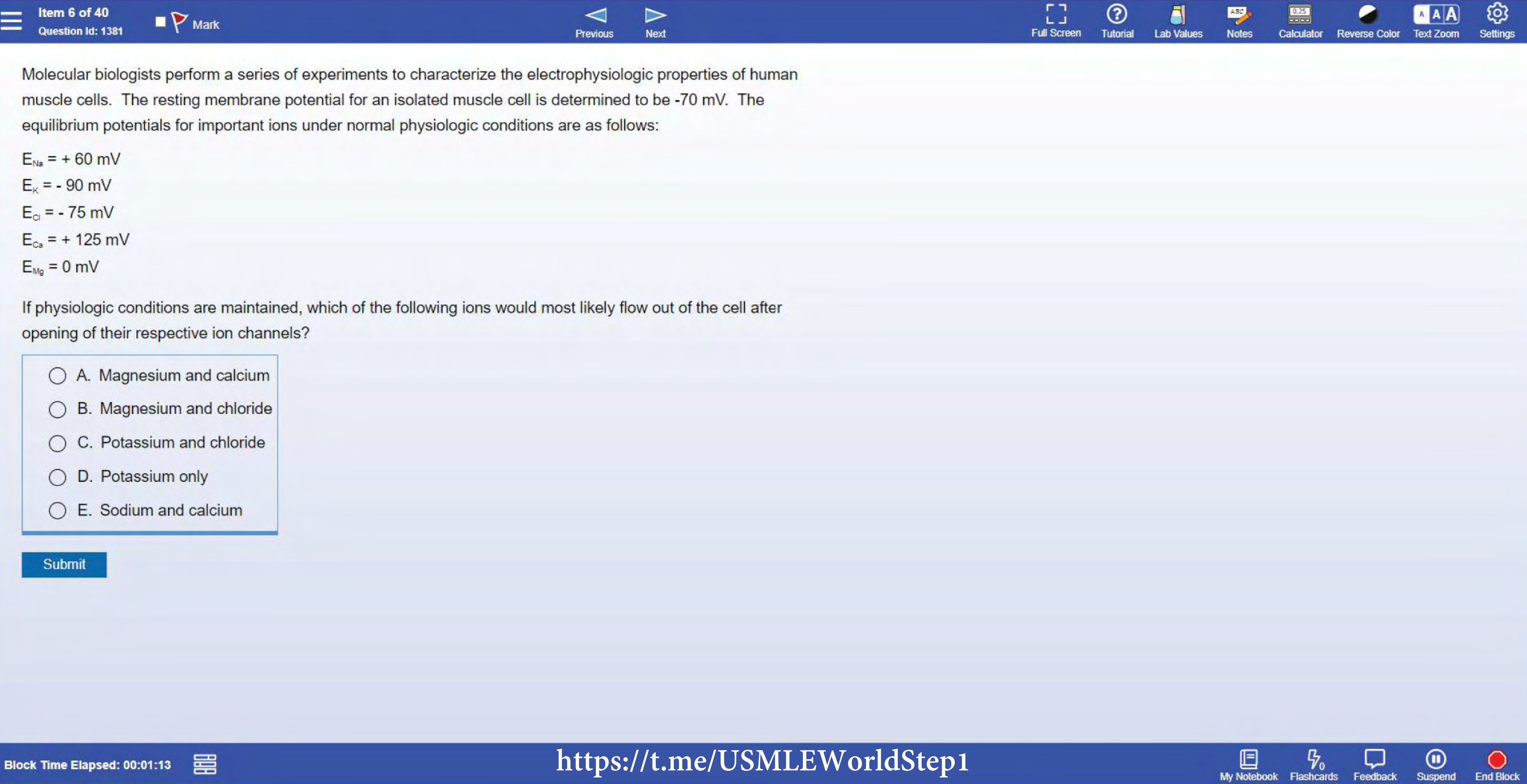
Item 6 of 40
Question Id: 1381
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Molecular biologists perform a series of experiments to characterize the electrophysiologic properties of human muscle cells. The resting membrane potential for an isolated muscle cell is determined to be -70 mV. The equilibrium potentials for important ions under normal physiologic conditions are as follows:

E_{Na} = + 60 mV
E_{K} = - 90 mV
E_{Cl} = - 75 mV
E_{Ca} = + 125 mV
E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

○ A. Magnesium and calcium
○ B. Magnesium and chloride
○ C. Potassium and chloride
○ D. Potassium only
○ E. Sodium and calcium

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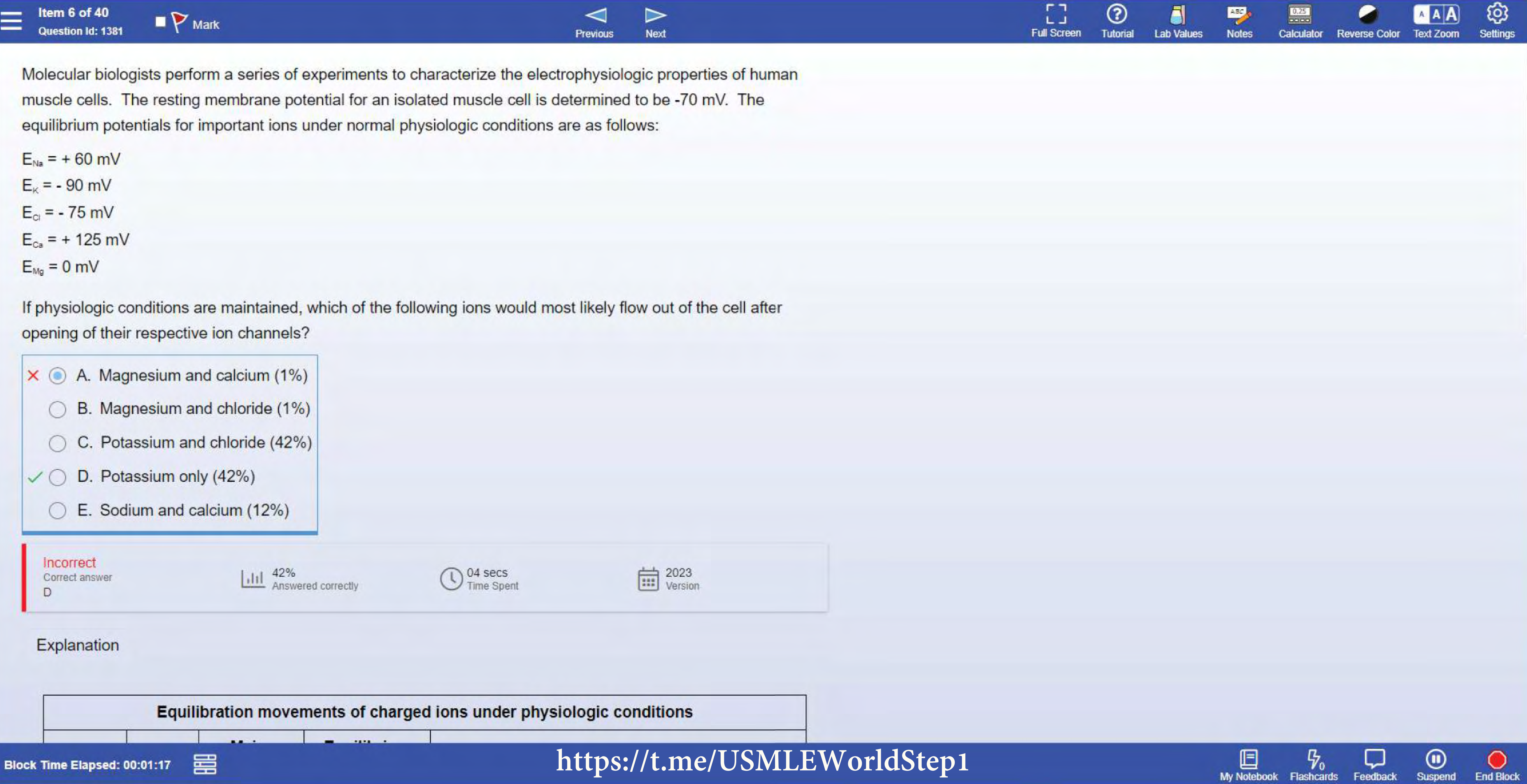
Block Time Elapsed: 00:01:13
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 6 of 40
Question Id: 1381
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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E_{Na} = + 60 mV
E_{K} = - 90 mV
E_{Cl} = - 75 mV
E_{Ca} = + 125 mV
E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

- ✗ ● A. Magnesium and calcium (1%)
- ○ B. Magnesium and chloride (1%)
- ○ C. Potassium and chloride (42%)
- ✓ ○ D. Potassium only (42%)
- ○ E. Sodium and calcium (12%)

Incorrect
Correct answer
D

42%
Answered correctly

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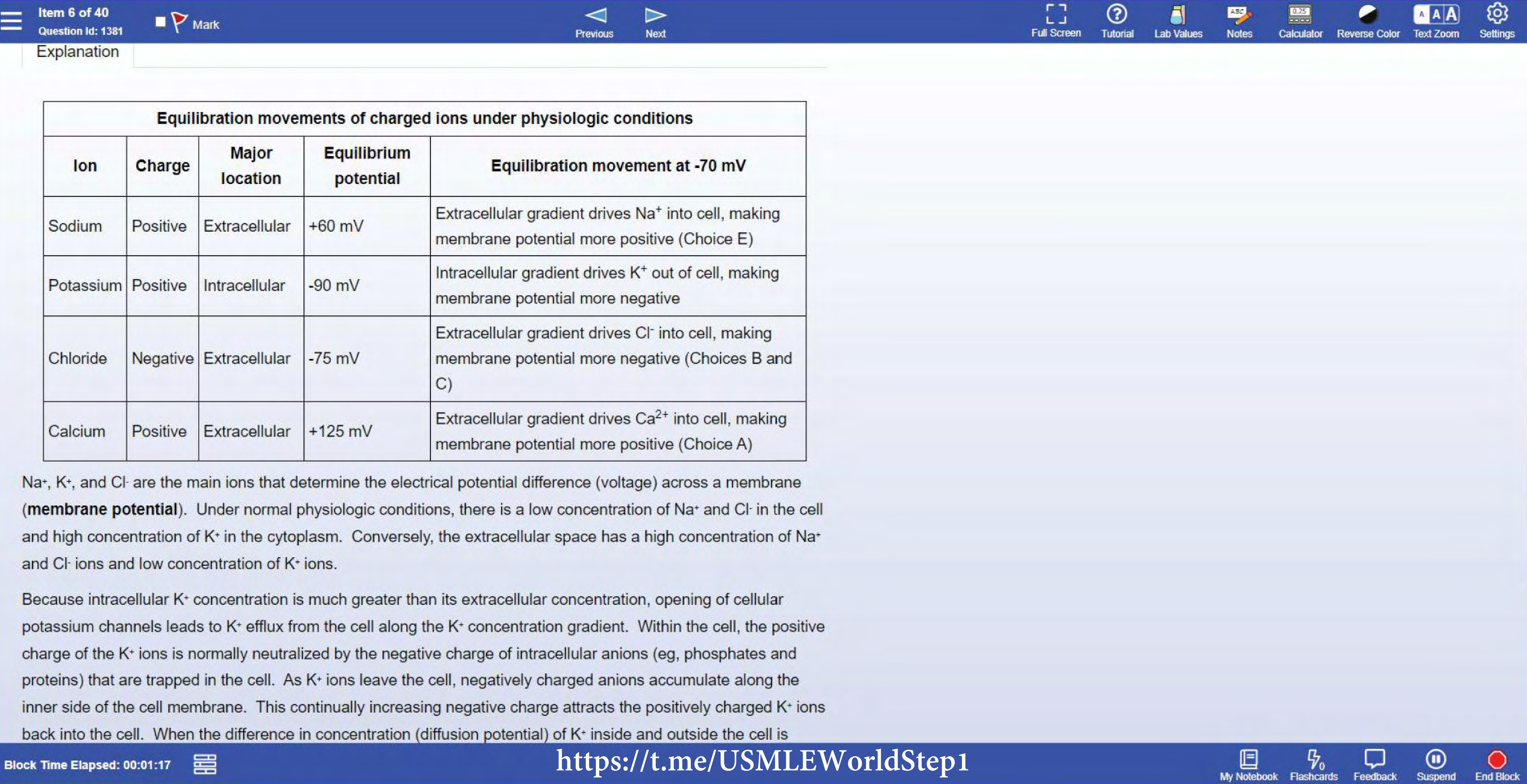
2023
Version

Explanation

Equilibration movements of charged ions under physiologic conditions

Block Time Elapsed: 00:01:17
My Notebook
Flashcards
Feedback
Suspend
End Block

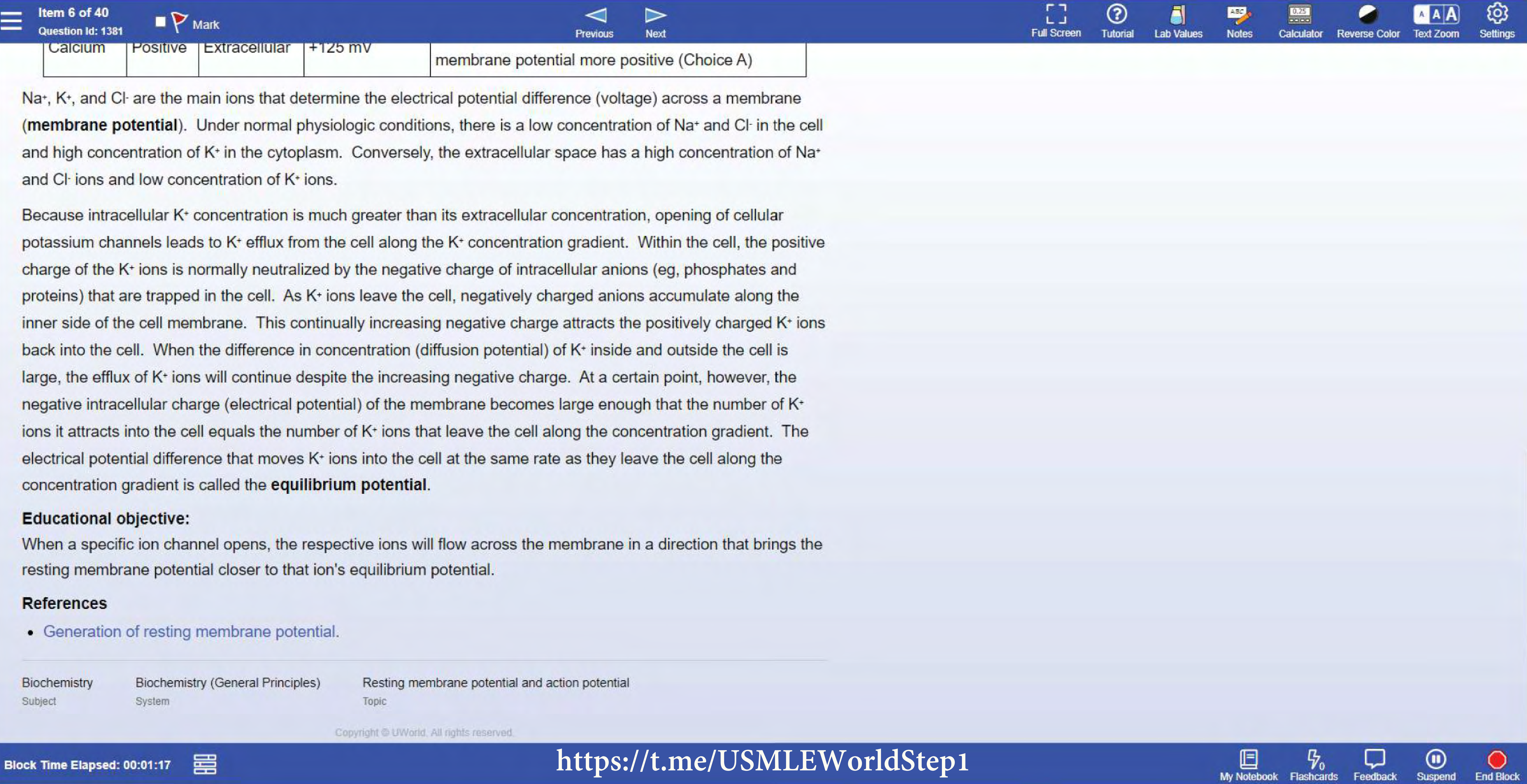

Item 6 of 40
Question Id: 1381
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:01:17
My Notebook
Flashcards
Feedback
Suspend
End Block

Equilibration movements of charged ions under physiologic conditions

Ion	Charge	Major location	Equilibrium potential	Equilibration movement at -70 mV
Sodium	Positive	Extracellular	+60 mV	Extracellular gradient drives Na$^+$ into cell, making membrane potential more positive (Choice E)
Potassium	Positive	Intracellular	-90 mV	Intracellular gradient drives K$^+$ out of cell, making membrane potential more negative
Chloride	Negative	Extracellular	-75 mV	Extracellular gradient drives Cl$^-$ into cell, making membrane potential more negative (Choices B and C)
Calcium	Positive	Extracellular	+125 mV	Extracellular gradient drives Ca^{2+} into cell, making membrane potential more positive (Choice A)

Na$^+$, K$^+$, and Cl$^-$ are the main ions that determine the electrical potential difference (voltage) across a membrane (**membrane potential**). Under normal physiologic conditions, there is a low concentration of Na$^+$ and Cl$^-$ in the cell and high concentration of K$^+$ in the cytoplasm. Conversely, the extracellular space has a high concentration of Na$^+$ and Cl$^-$ ions and low concentration of K$^+$ ions.

Because intracellular K$^+$ concentration is much greater than its extracellular concentration, opening of cellular potassium channels leads to K$^+$ efflux from the cell along the K$^+$ concentration gradient. Within the cell, the positive charge of the K$^+$ ions is normally neutralized by the negative charge of intracellular anions (eg, phosphates and proteins) that are trapped in the cell. As K$^+$ ions leave the cell, negatively charged anions accumulate along the inner side of the cell membrane. This continually increasing negative charge attracts the positively charged K$^+$ ions back into the cell. When the difference in concentration (diffusion potential) of K$^+$ inside and outside the cell is



Calcium	Positive	Extracellular	+125 mV	membrane potential more positive (Choice A)

Na^+, K^+, and Cl^- are the main ions that determine the electrical potential difference (voltage) across a membrane (**membrane potential**). Under normal physiologic conditions, there is a low concentration of Na^+ and Cl^- in the cell and high concentration of K^+ in the cytoplasm. Conversely, the extracellular space has a high concentration of Na^+ and Cl^- ions and low concentration of K^+ ions.

Because intracellular K^+ concentration is much greater than its extracellular concentration, opening of cellular potassium channels leads to K^+ efflux from the cell along the K^+ concentration gradient. Within the cell, the positive charge of the K^+ ions is normally neutralized by the negative charge of intracellular anions (eg, phosphates and proteins) that are trapped in the cell. As K^+ ions leave the cell, negatively charged anions accumulate along the inner side of the cell membrane. This continually increasing negative charge attracts the positively charged K^+ ions back into the cell. When the difference in concentration (diffusion potential) of K^+ inside and outside the cell is large, the efflux of K^+ ions will continue despite the increasing negative charge. At a certain point, however, the negative intracellular charge (electrical potential) of the membrane becomes large enough that the number of K^+ ions it attracts into the cell equals the number of K^+ ions that leave the cell along the concentration gradient. The electrical potential difference that moves K^+ ions into the cell at the same rate as they leave the cell along the concentration gradient is called the **equilibrium potential**.

Educational objective:
When a specific ion channel opens, the respective ions will flow across the membrane in a direction that brings the resting membrane potential closer to that ion's equilibrium potential.

References

- Generation of resting membrane potential.

Biochemistry	Biochemistry (General Principles)	Resting membrane potential and action potential
Subject	System	Topic

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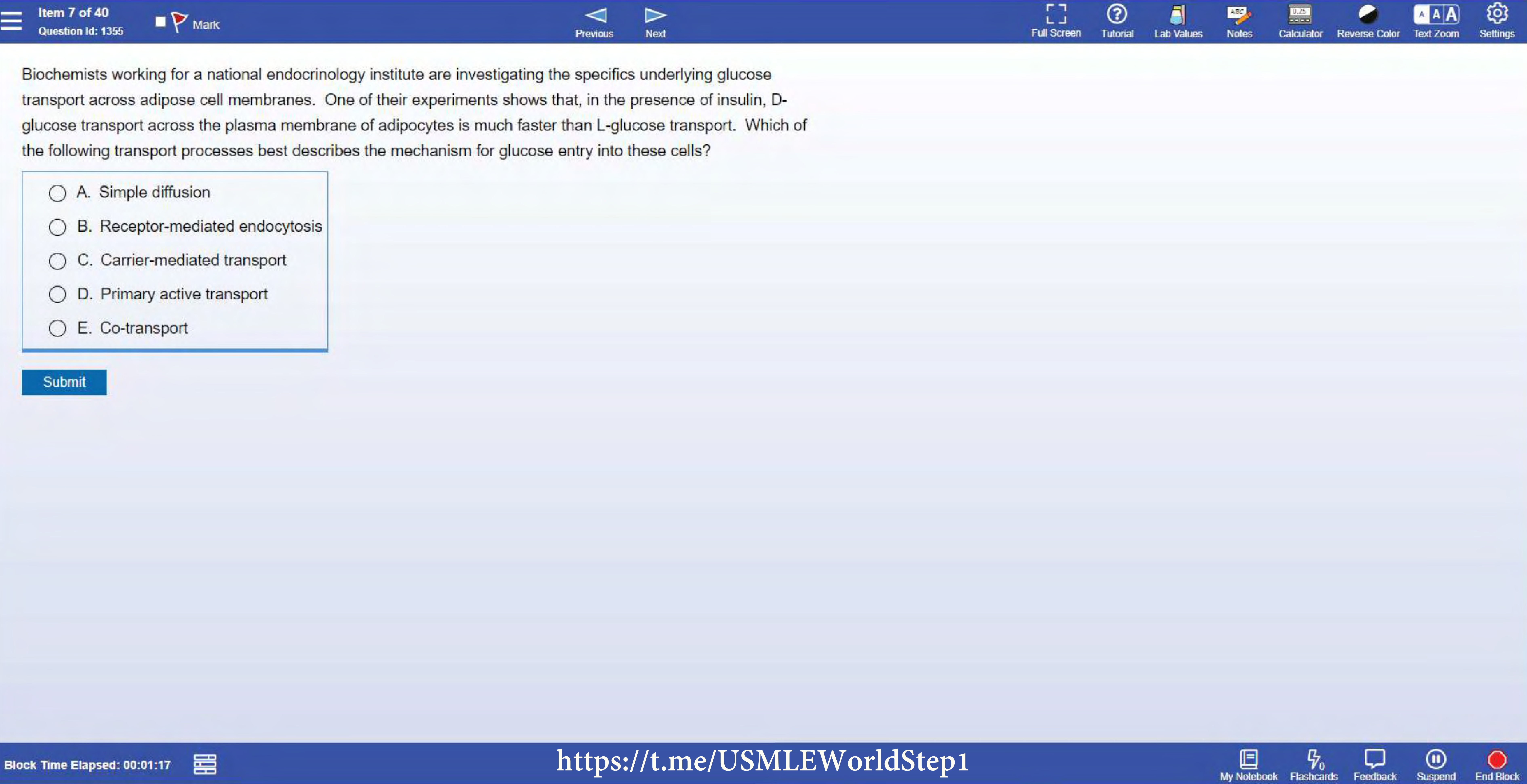
Item 7 of 40
Question Id: 1355
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:01:17
My Notebook
Flashcards
Feedback
Suspend
End Block

Biochemists working for a national endocrinology institute are investigating the specifics underlying glucose transport across adipose cell membranes. One of their experiments shows that, in the presence of insulin, D-glucose transport across the plasma membrane of adipocytes is much faster than L-glucose transport. Which of the following transport processes best describes the mechanism for glucose entry into these cells?

○ A. Simple diffusion

○ B. Receptor-mediated endocytosis

○ C. Carrier-mediated transport

○ D. Primary active transport

○ E. Co-transport

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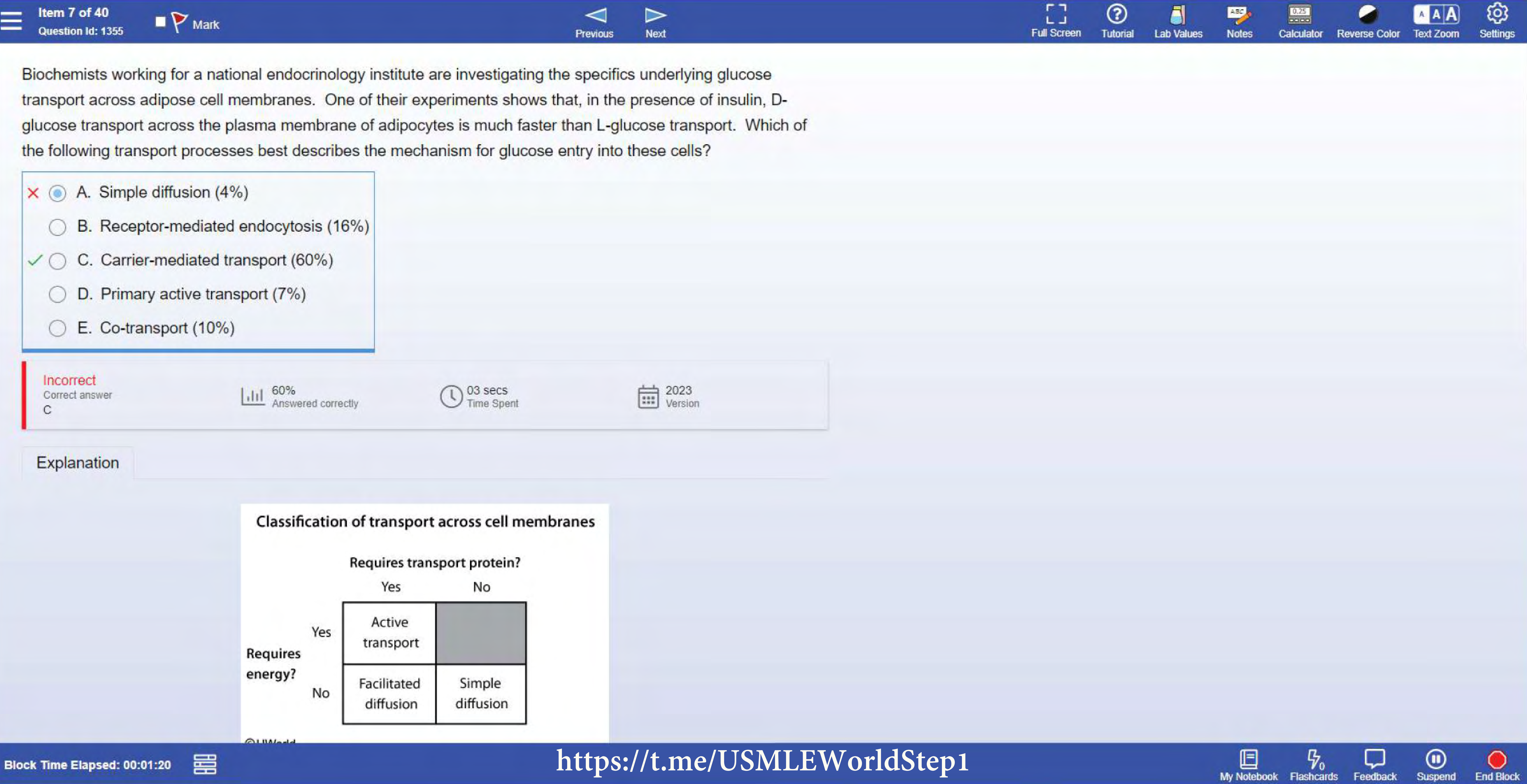
Item 7 of 40
Question Id: 1355
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Biochemists working for a national endocrinology institute are investigating the specifics underlying glucose transport across adipose cell membranes. One of their experiments shows that, in the presence of insulin, D-glucose transport across the plasma membrane of adipocytes is much faster than L-glucose transport. Which of the following transport processes best describes the mechanism for glucose entry into these cells?

- ✗ ● A. Simple diffusion (4%)
- ○ B. Receptor-mediated endocytosis (16%)
- ✓ ○ C. Carrier-mediated transport (60%)
- ○ D. Primary active transport (7%)
- ○ E. Co-transport (10%)

Incorrect
Correct answer
C

60%
Answered correctly

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Time Spent

2023
Version

Explanation

Classification of transport across cell membranes

		Requires transport protein? Yes	Requires transport protein? No
Requires energy?	Yes	Active transport	▨
Requires energy?	No	Facilitated diffusion	Simple diffusion

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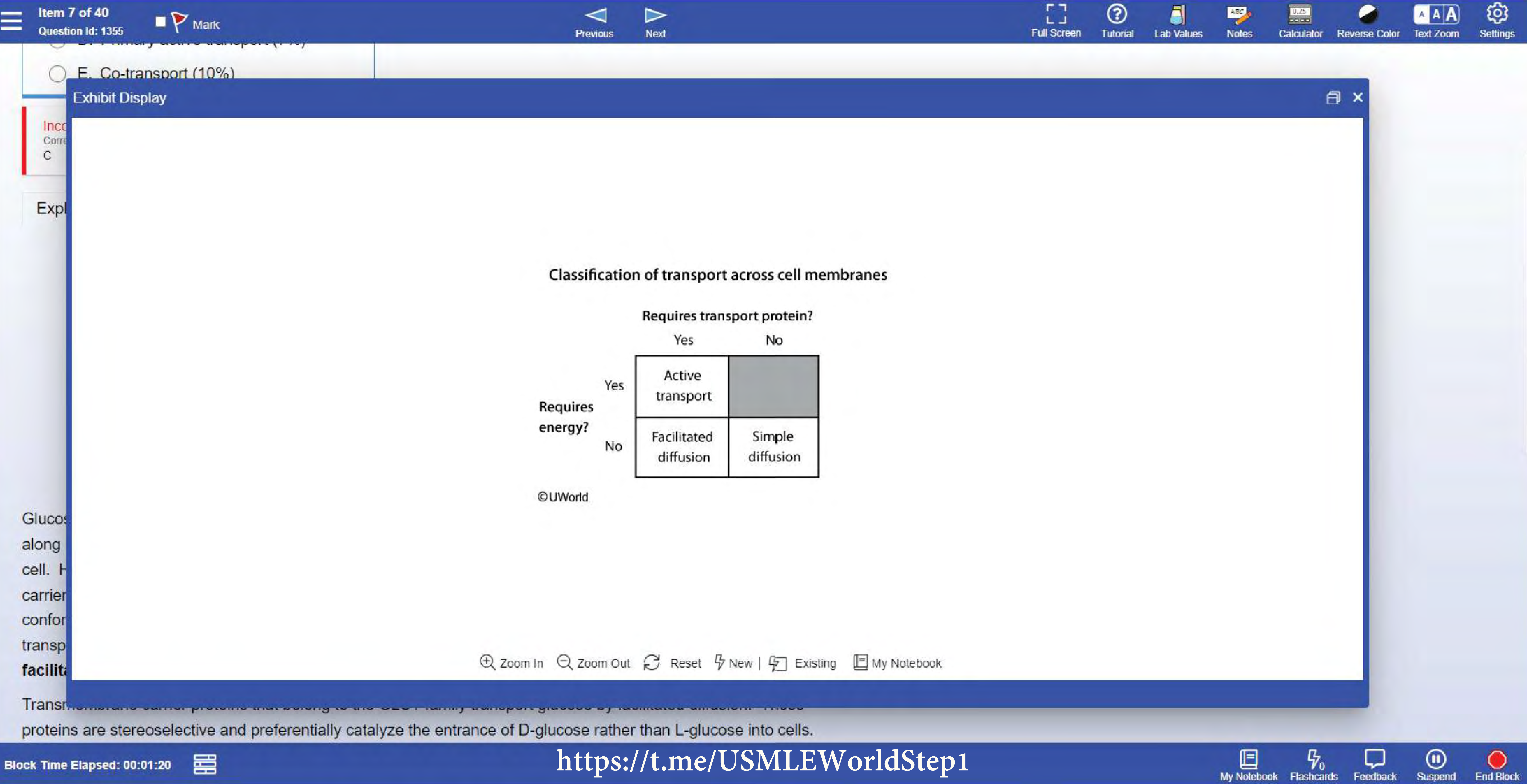
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 7 of 40
Question Id: 1355
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:01:20
My Notebook
Flashcards
Feedback
Suspend
End Block

○ E. Co-transport (10%)

Classification of transport across cell membranes

		Requires transport protein?	
		Yes	No
Requires energy?	Yes	Active transport	▨
	No	Facilitated diffusion	Simple diffusion

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proteins are stereoselective and preferentially catalyze the entrance of D-glucose rather than L-glucose into cells.

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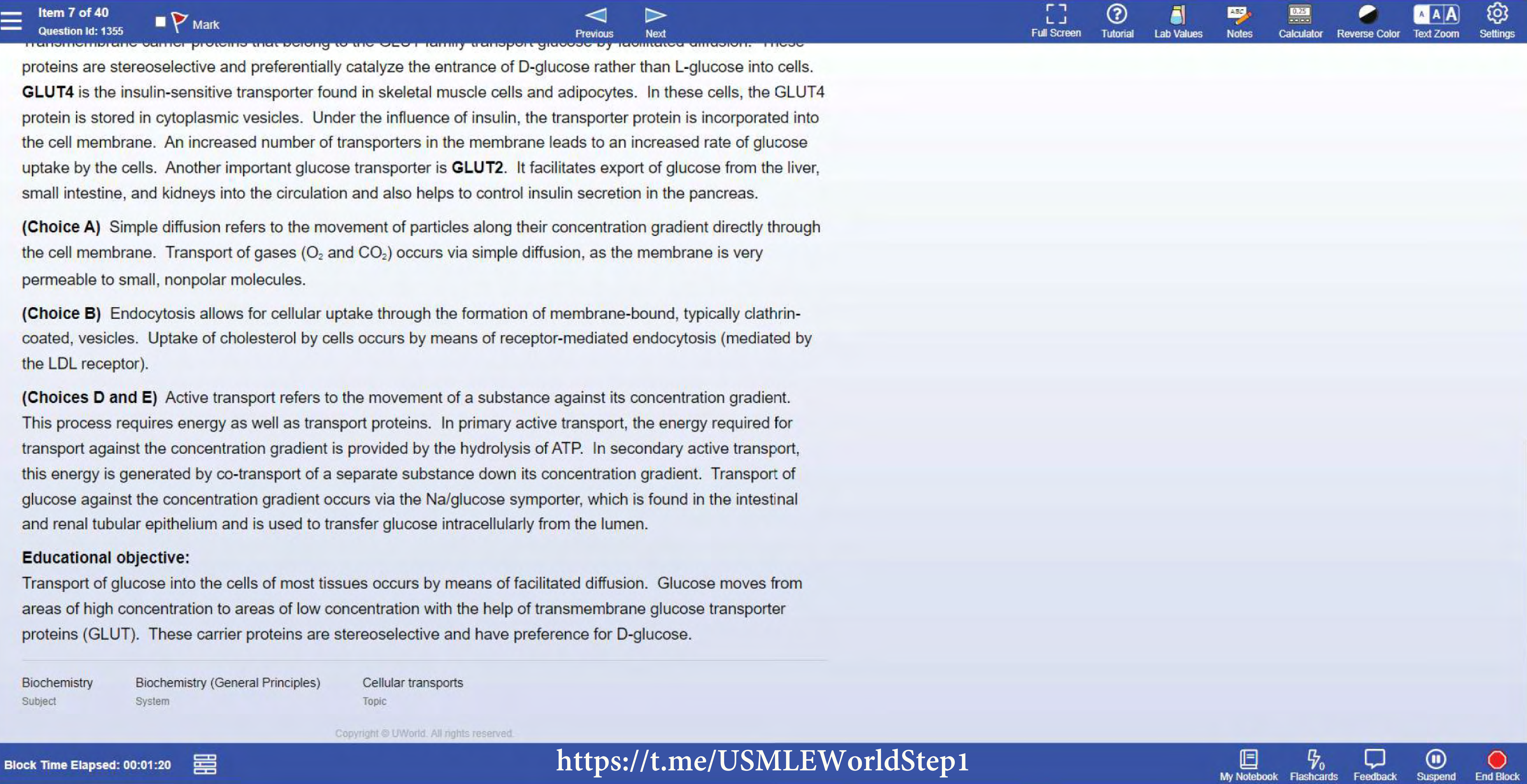
Glucose is the major source of energy for all cells of the body. In the majority of tissues, glucose transport occurs along its concentration gradient, from higher concentrations outside the cell toward lower concentrations inside the cell. However, glucose cannot passively diffuse across the cell membrane in any significant amount and requires carrier proteins to aid its crossing. Transport across the cell membrane by carrier proteins (which undergo conformational changes as the substrate is transported, unlike channel proteins) is termed carrier-mediated transport. Transport that is facilitated by transmembrane proteins without the expenditure of energy is called **facilitated diffusion**.

Transmembrane carrier proteins that belong to the GLUT family transport glucose by facilitated diffusion. These proteins are stereoselective and preferentially catalyze the entrance of D-glucose rather than L-glucose into cells. **GLUT4** is the insulin-sensitive transporter found in skeletal muscle cells and adipocytes. In these cells, the GLUT4 protein is stored in cytoplasmic vesicles. Under the influence of insulin, the transporter protein is incorporated into the cell membrane. An increased number of transporters in the membrane leads to an increased rate of glucose uptake by the cells. Another important glucose transporter is **GLUT2**. It facilitates export of glucose from the liver, small intestine, and kidneys into the circulation and also helps to control insulin secretion in the pancreas.

(Choice A) Simple diffusion refers to the movement of particles along their concentration gradient directly through the cell membrane. Transport of gases (O_2 and CO_2) occurs via simple diffusion, as the membrane is very permeable to small, nonpolar molecules.

(Choice B) Endocytosis allows for cellular uptake through the formation of membrane-bound, typically clathrin-coated, vesicles. Uptake of cholesterol by cells occurs by means of receptor-mediated endocytosis (mediated by the LDL receptor).

(Choices D and E) Active transport refers to the movement of a substance against its concentration gradient. This process requires energy as well as transport proteins. In primary active transport, the energy required for transport against the concentration gradient is provided by the hydrolysis of ATP. In secondary active transport, this energy is generated by co-transport of a separate substance down its concentration gradient. Transport of glucose against the concentration gradient occurs via the Na/glucose symporter, which is found in the intestinal



proteins are stereoselective and preferentially catalyze the entrance of D-glucose rather than L-glucose into cells. **GLUT4** is the insulin-sensitive transporter found in skeletal muscle cells and adipocytes. In these cells, the GLUT4 protein is stored in cytoplasmic vesicles. Under the influence of insulin, the transporter protein is incorporated into the cell membrane. An increased number of transporters in the membrane leads to an increased rate of glucose uptake by the cells. Another important glucose transporter is **GLUT2**. It facilitates export of glucose from the liver, small intestine, and kidneys into the circulation and also helps to control insulin secretion in the pancreas.

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Educational objective:

Transport of glucose into the cells of most tissues occurs by means of facilitated diffusion. Glucose moves from areas of high concentration to areas of low concentration with the help of transmembrane glucose transporter proteins (GLUT). These carrier proteins are stereoselective and have preference for D-glucose.

Biochemistry	Biochemistry (General Principles)	Cellular transports
Subject	System	Topic

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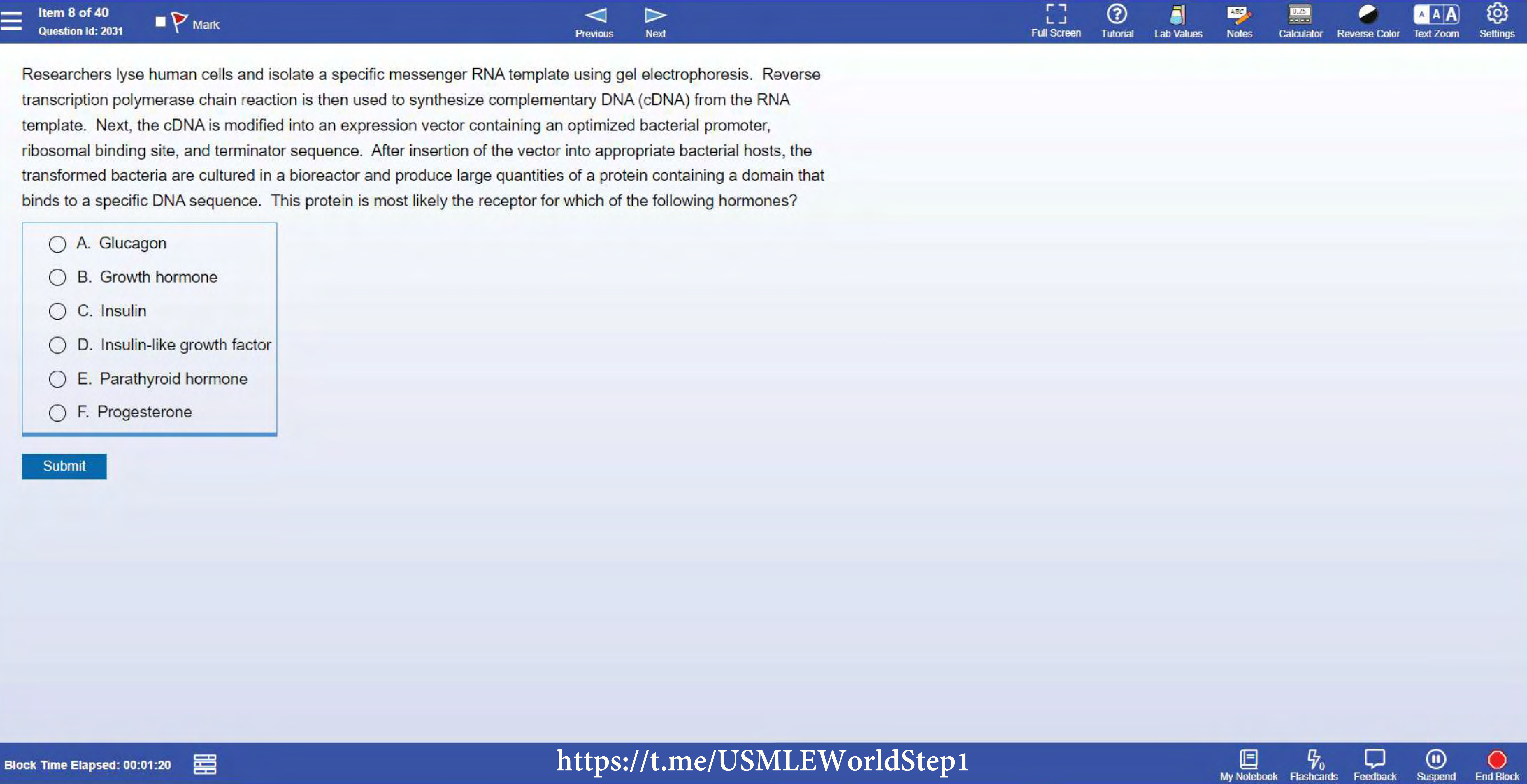
Item 8 of 40
Question Id: 2031
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Researchers lyse human cells and isolate a specific messenger RNA template using gel electrophoresis. Reverse transcription polymerase chain reaction is then used to synthesize complementary DNA (cDNA) from the RNA template. Next, the cDNA is modified into an expression vector containing an optimized bacterial promoter, ribosomal binding site, and terminator sequence. After insertion of the vector into appropriate bacterial hosts, the transformed bacteria are cultured in a bioreactor and produce large quantities of a protein containing a domain that binds to a specific DNA sequence. This protein is most likely the receptor for which of the following hormones?

○ A. Glucagon
○ B. Growth hormone
○ C. Insulin
○ D. Insulin-like growth factor
○ E. Parathyroid hormone
○ F. Progesterone

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My Notebook
Flashcards
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Suspend
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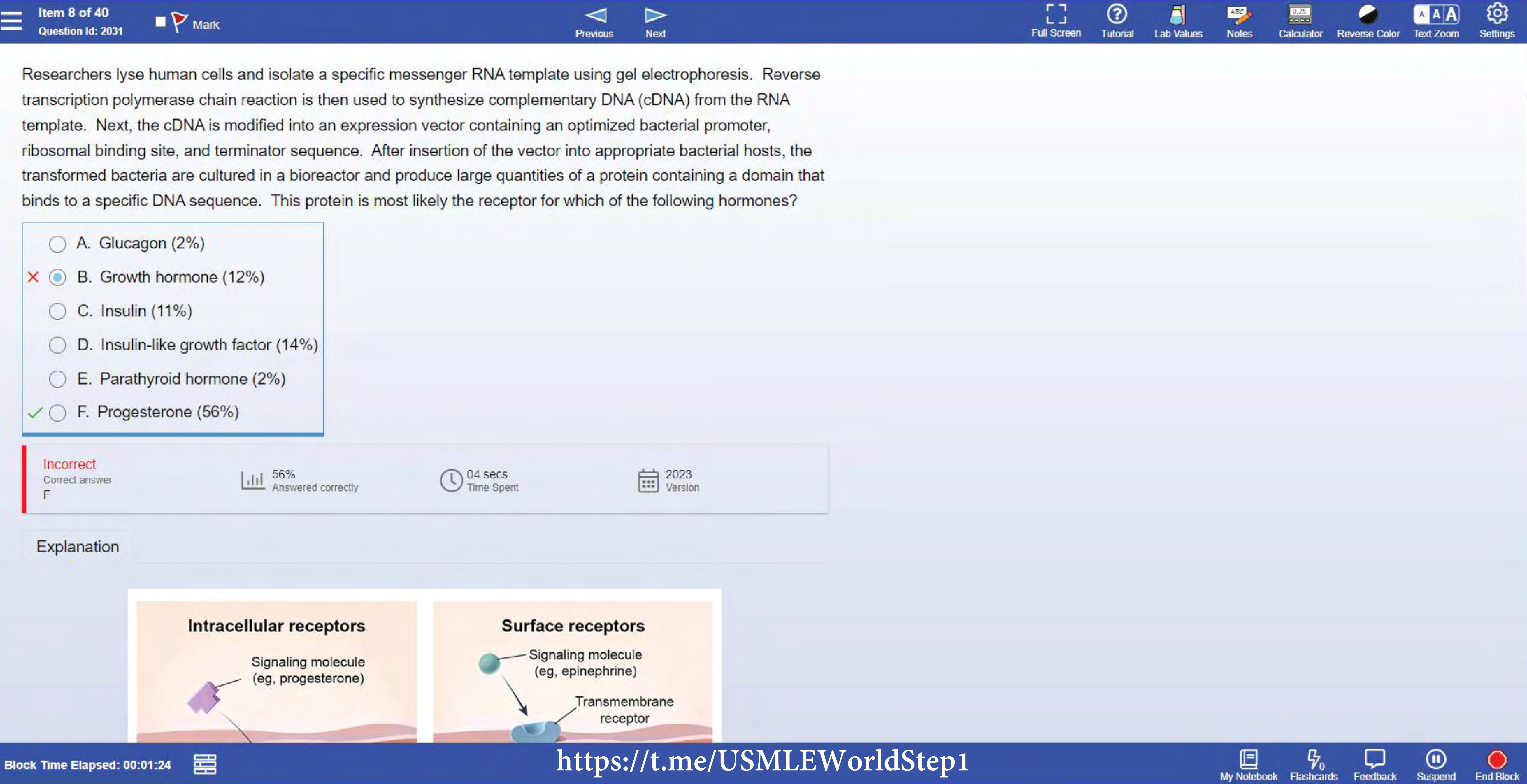
Item 8 of 40
Question Id: 2031
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ A. Glucagon (2%)
✗ ● B. Growth hormone (12%)
○ C. Insulin (11%)
○ D. Insulin-like growth factor (14%)
○ E. Parathyroid hormone (2%)
✓ ○ F. Progesterone (56%)

Incorrect
Correct answer
F

56%
Answered correctly

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2023
Version

Explanation

Intracellular receptors
Signaling molecule
(eg, progesterone)
Surface receptors
Signaling molecule
(eg, epinephrine)
Transmembrane
receptor

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My Notebook
Flashcards
Feedback
Suspend
End Block

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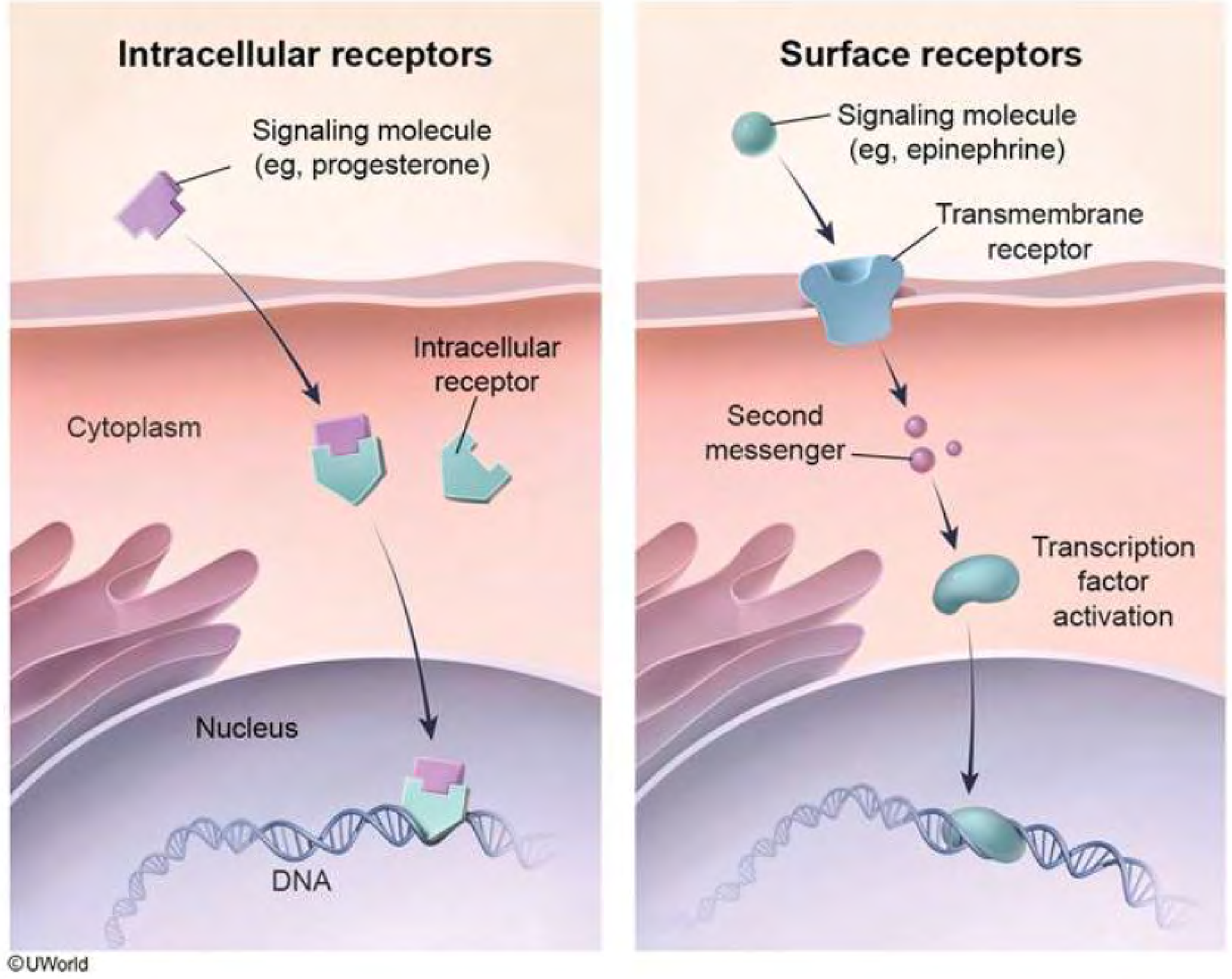
Intracellular receptors
Signaling molecule (eg, progesterone)
Intracellular receptor
Cytoplasm
Nucleus
DNA
Surface receptors
Signaling molecule (eg, epinephrine)
Transmembrane receptor
Second messenger
Transcription factor activation
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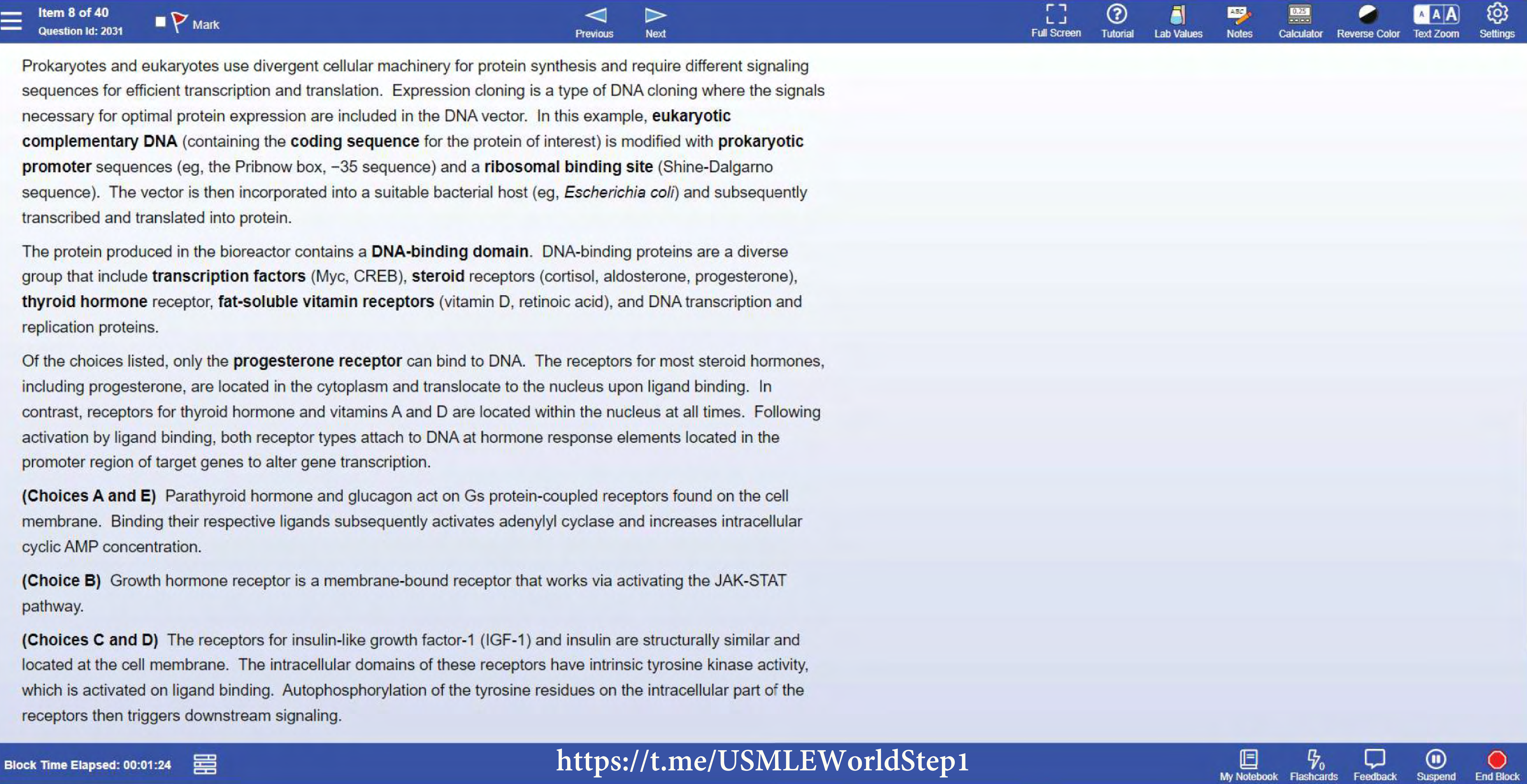
transcribed and translated into protein.



Prokaryotes and eukaryotes use divergent cellular machinery for protein synthesis and require different signaling sequences for efficient transcription and translation. Expression cloning is a type of DNA cloning where the signals necessary for optimal protein expression are included in the DNA vector. In this example, **eukaryotic complementary DNA** (containing the **coding sequence** for the protein of interest) is modified with **prokaryotic promoter** sequences (eg, the Pribnow box, −35 sequence) and a **ribosomal binding site** (Shine-Dalgarno sequence). The vector is then incorporated into a suitable bacterial host (eg, *Escherichia coli*) and subsequently transcribed and translated into protein.

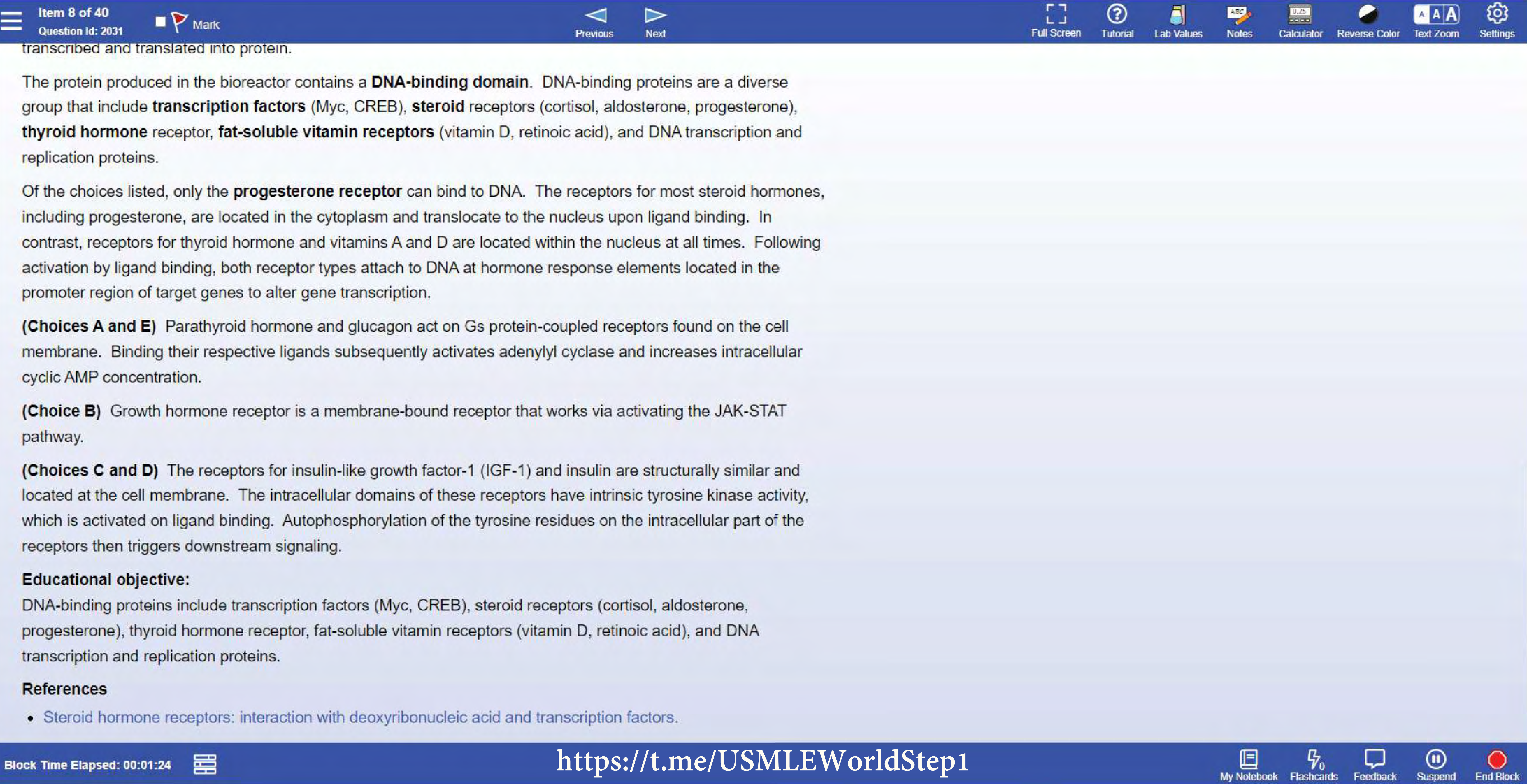
The protein produced in the bioreactor contains a **DNA-binding domain**. DNA-binding proteins are a diverse group that include **transcription factors** (Myc, CREB), **steroid** receptors (cortisol, aldosterone, progesterone), **thyroid hormone** receptor, **fat-soluble vitamin receptors** (vitamin D, retinoic acid), and DNA transcription and replication proteins.

Of the choices listed, only the **progesterone receptor** can bind to DNA. The receptors for most steroid hormones, including progesterone, are located in the cytoplasm and translocate to the nucleus upon ligand binding. In contrast, receptors for thyroid hormone and vitamins A and D are located within the nucleus at all times. Following activation by ligand binding, both receptor types attach to DNA at hormone response elements located in the promoter region of target genes to alter gene transcription.

(Choices A and E) Parathyroid hormone and glucagon act on Gs protein-coupled receptors found on the cell membrane. Binding their respective ligands subsequently activates adenylyl cyclase and increases intracellular cyclic AMP concentration.

(Choice B) Growth hormone receptor is a membrane-bound receptor that works via activating the JAK-STAT pathway.

(Choices C and D) The receptors for insulin-like growth factor-1 (IGF-1) and insulin are structurally similar and located at the cell membrane. The intracellular domains of these receptors have intrinsic tyrosine kinase activity, which is activated on ligand binding. Autophosphorylation of the tyrosine residues on the intracellular part of the receptors then triggers downstream signaling.



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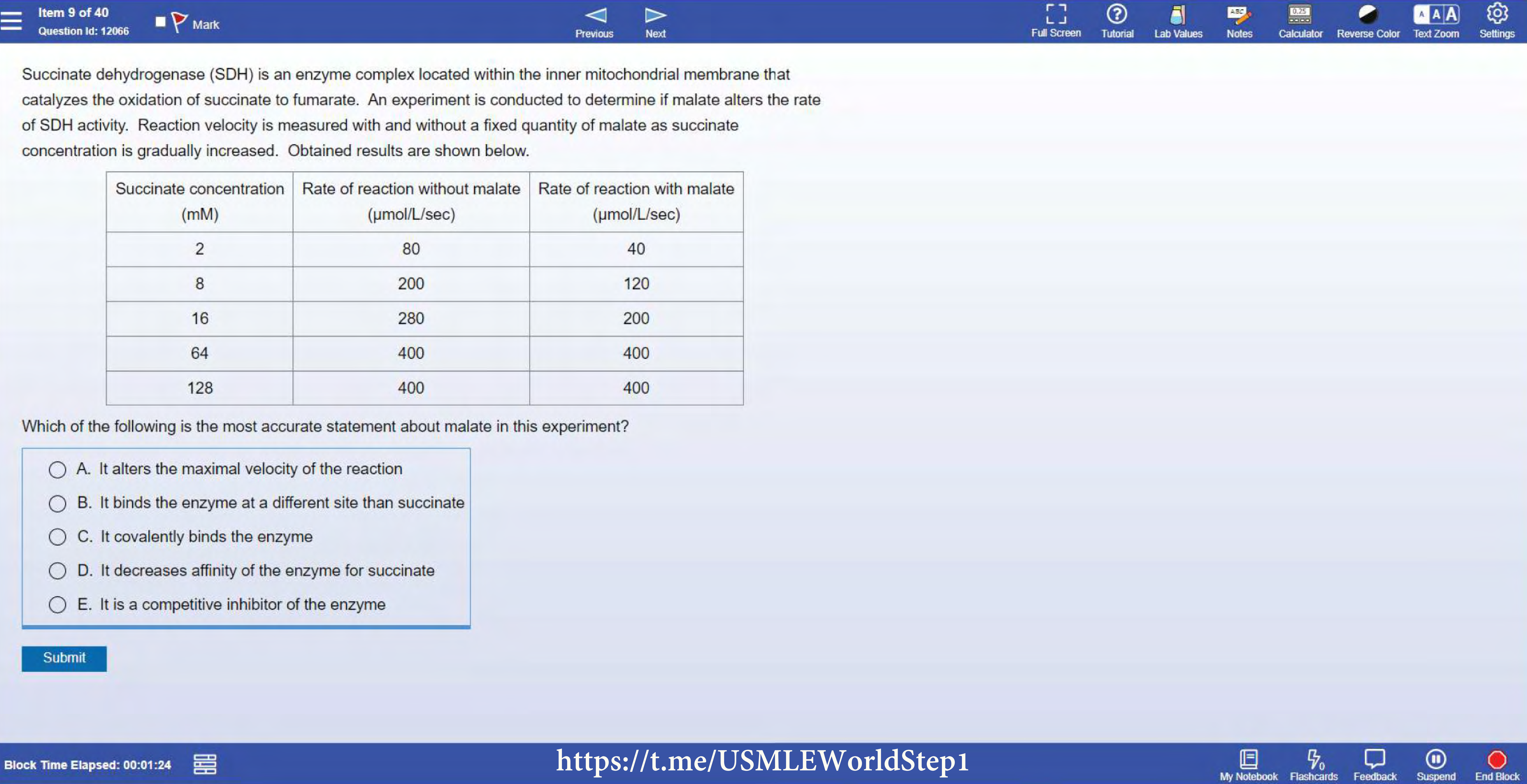
Educational objective:

DNA-binding proteins include transcription factors (Myc, CREB), steroid receptors (cortisol, aldosterone, progesterone), thyroid hormone receptor, fat-soluble vitamin receptors (vitamin D, retinoic acid), and DNA transcription and replication proteins.

References

- Steroid hormone receptors: interaction with deoxyribonucleic acid and transcription factors.


Item 9 of 40
Question Id: 12066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Succinate dehydrogenase (SDH) is an enzyme complex located within the inner mitochondrial membrane that catalyzes the oxidation of succinate to fumarate. An experiment is conducted to determine if malate alters the rate of SDH activity. Reaction velocity is measured with and without a fixed quantity of malate as succinate concentration is gradually increased. Obtained results are shown below.

Succinate concentration (mM)	Rate of reaction without malate (μmol/L/sec)	Rate of reaction with malate (μmol/L/sec)
2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

○ A. It alters the maximal velocity of the reaction

○ B. It binds the enzyme at a different site than succinate

○ C. It covalently binds the enzyme

○ D. It decreases affinity of the enzyme for succinate

○ E. It is a competitive inhibitor of the enzyme

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Flashcards
Feedback
Suspend
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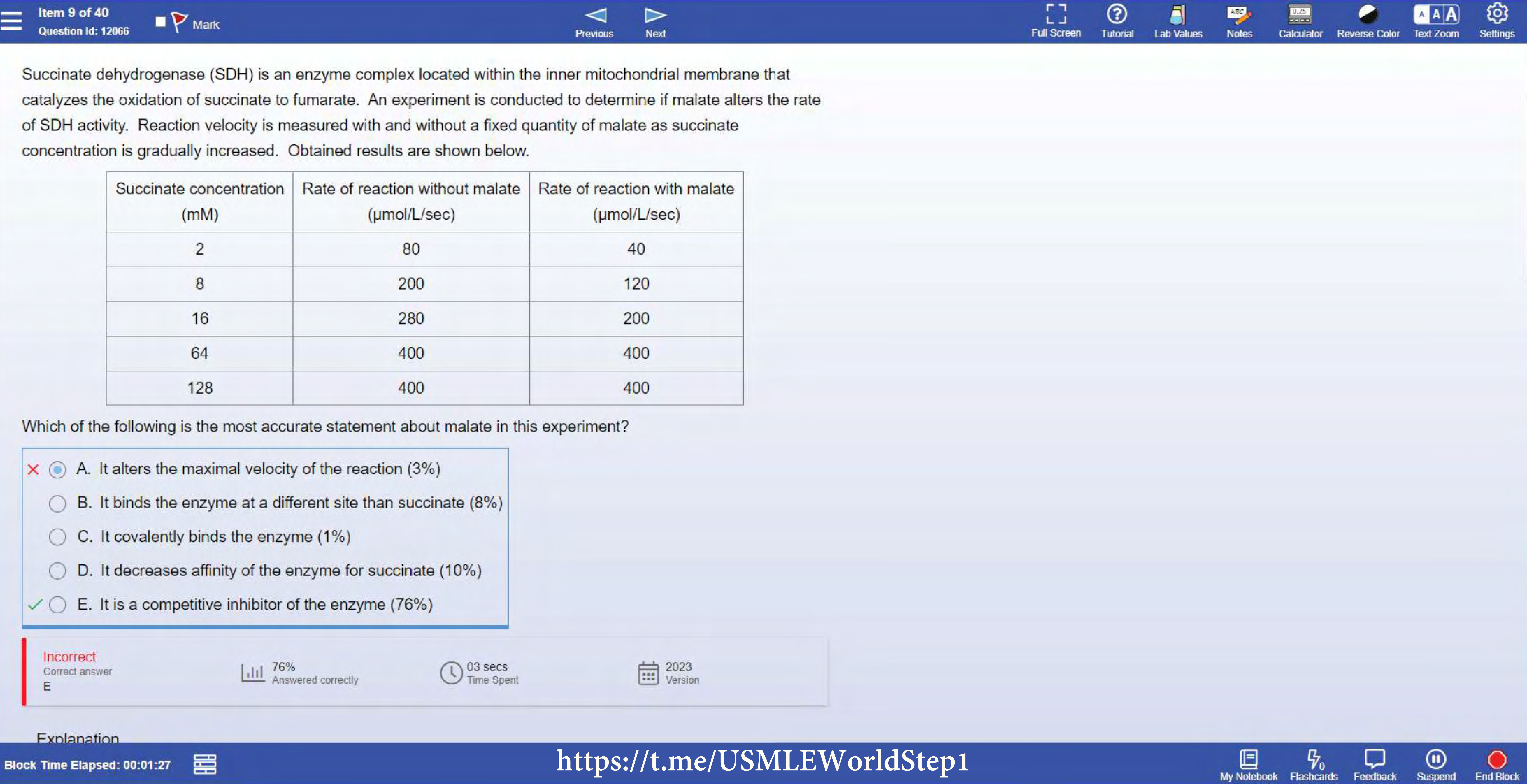
Item 9 of 40
Question Id: 12066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
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2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

✗ ● A. It alters the maximal velocity of the reaction (3%)

○ B. It binds the enzyme at a different site than succinate (8%)

○ C. It covalently binds the enzyme (1%)

○ D. It decreases affinity of the enzyme for succinate (10%)

✓ ○ E. It is a competitive inhibitor of the enzyme (76%)

Incorrect
Correct answer
E

76%
Answered correctly

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Explanation

Explanation

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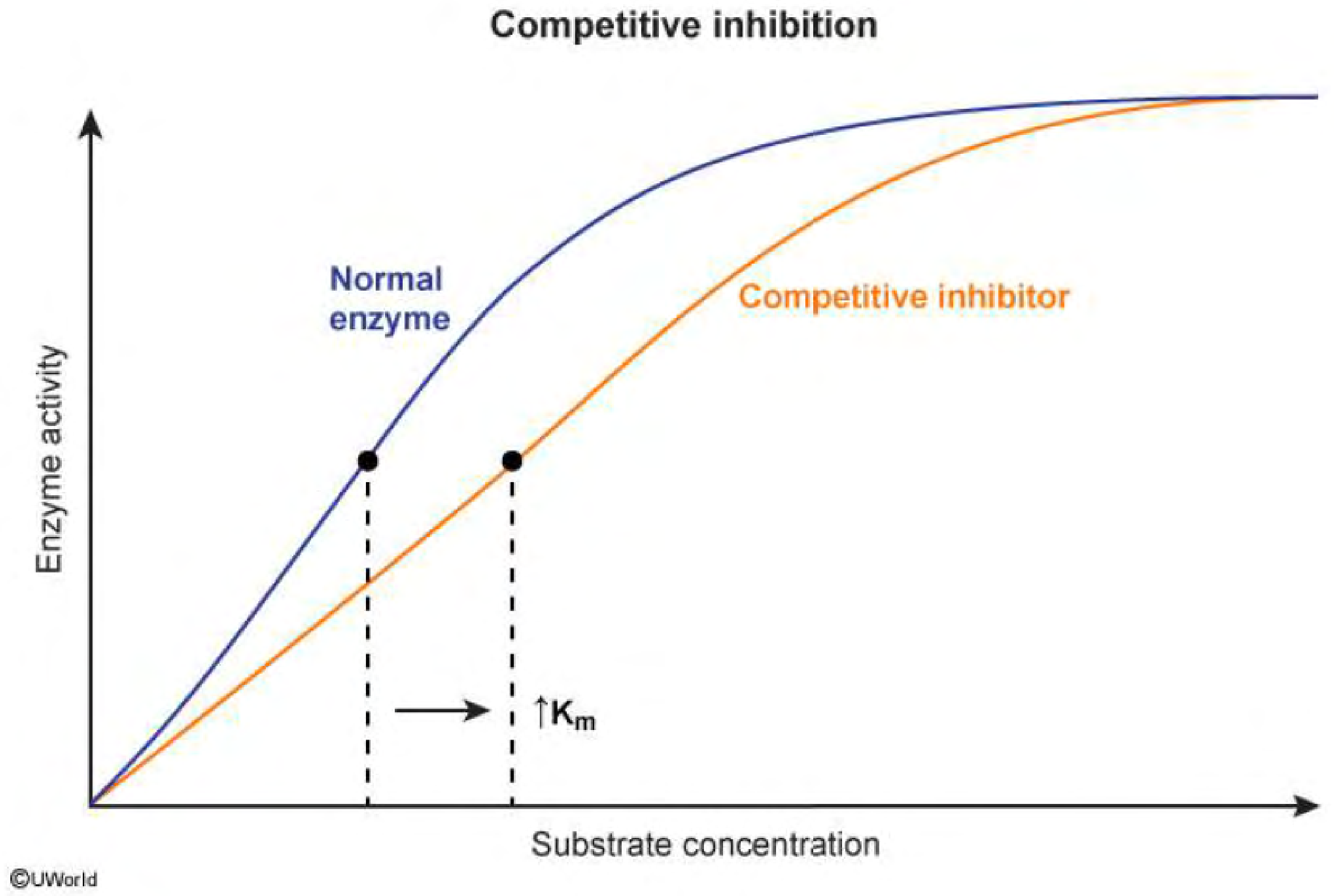

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Substrate concentration

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The Michaelis-Menten model describes the behavior of enzyme-driven reactions by comparing the rate of reaction (V) to the concentration of the substrate (S). Maximal velocity (V_{max}) represents the speed at which the reaction occurs when the enzyme's active sites are completely saturated with substrate. The Michaelis constant (K_m) defines the substrate concentration at which half of the enzyme's binding sites are occupied by substrate (½ V_{max}). Substrates with high affinity for the enzyme typically have a low K_m.

Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors (including malate) **bind at the active site** (substrate-binding pocket) and physically impede substrate binding. Because these inhibitors compete with the substrate for binding to the active site, additional substrate is required to reach ½ V_{max}, thereby **increasing apparent K_m**. Competitive inhibitors have no effect on enzyme function, and therefore **V_{max} is unchanged**.

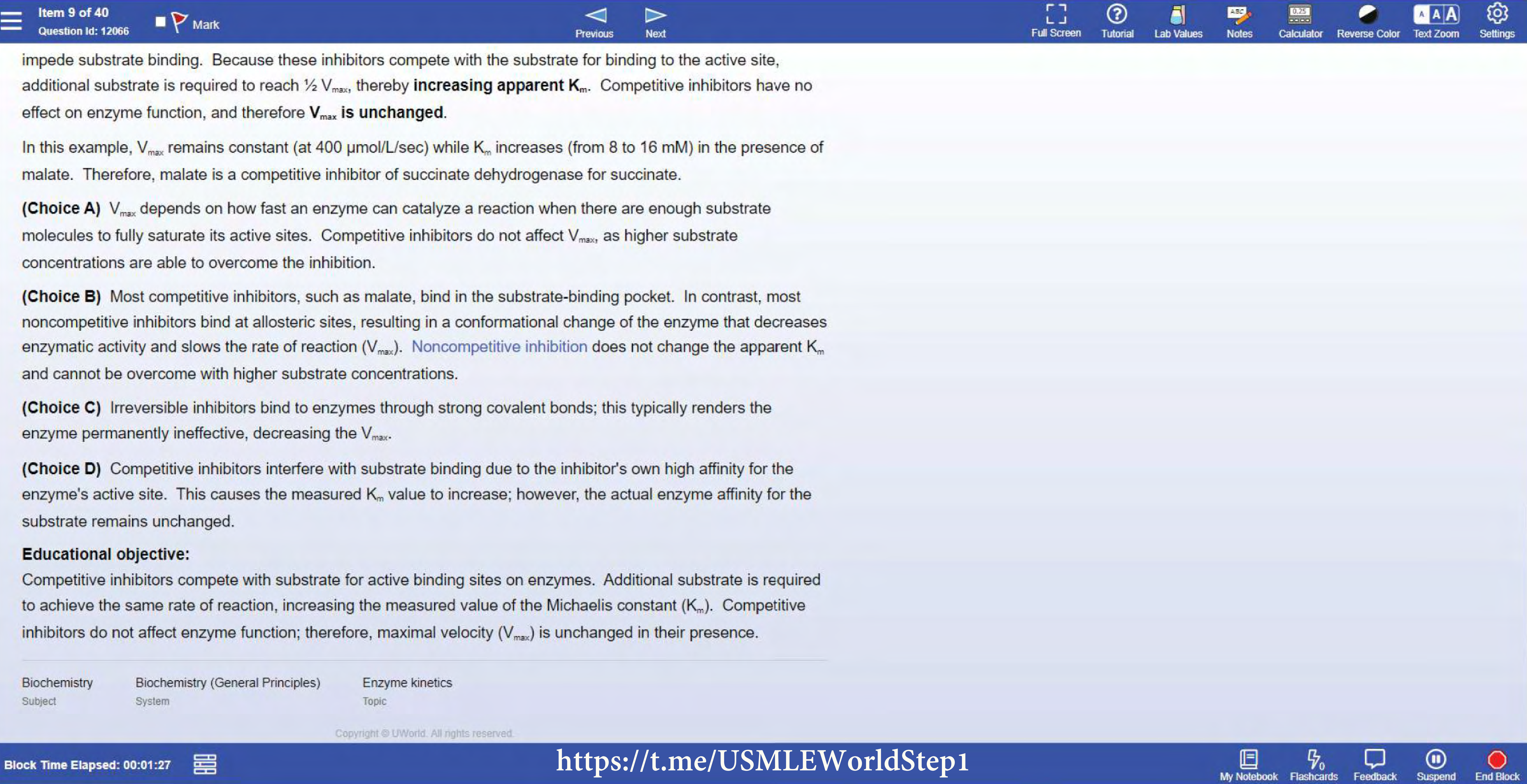
In this example, V_{max} remains constant (at 400 µmol/L/sec) while K_m increases (from 8 to 16 mM) in the presence of malate. Therefore, malate is a competitive inhibitor of succinate dehydrogenase for succinate.

(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate concentrations are able to overcome the inhibition.

(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the



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(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

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(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

Educational objective:

Competitive inhibitors compete with substrate for active binding sites on enzymes. Additional substrate is required to achieve the same rate of reaction, increasing the measured value of the Michaelis constant (K_m). Competitive inhibitors do not affect enzyme function; therefore, maximal velocity (V_{max}) is unchanged in their presence.

Biochemistry	Biochemistry (General Principles)	Enzyme kinetics
Subject	System	Topic

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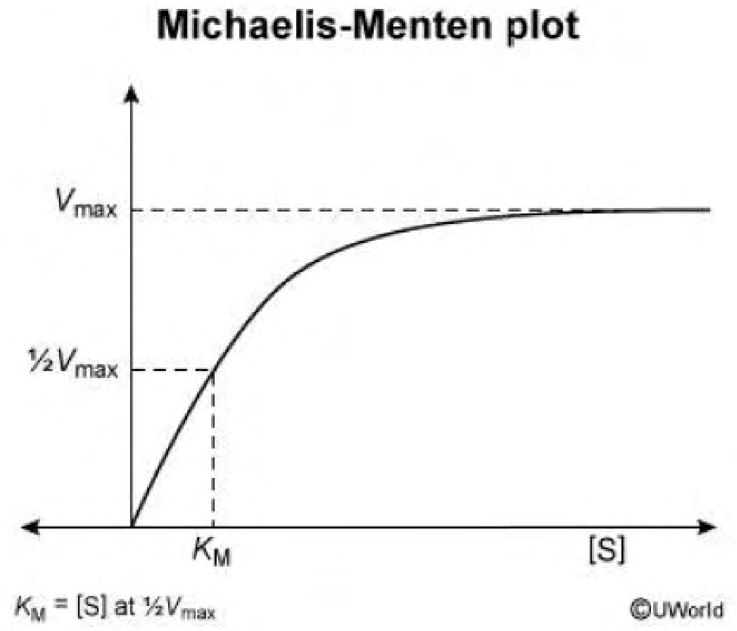

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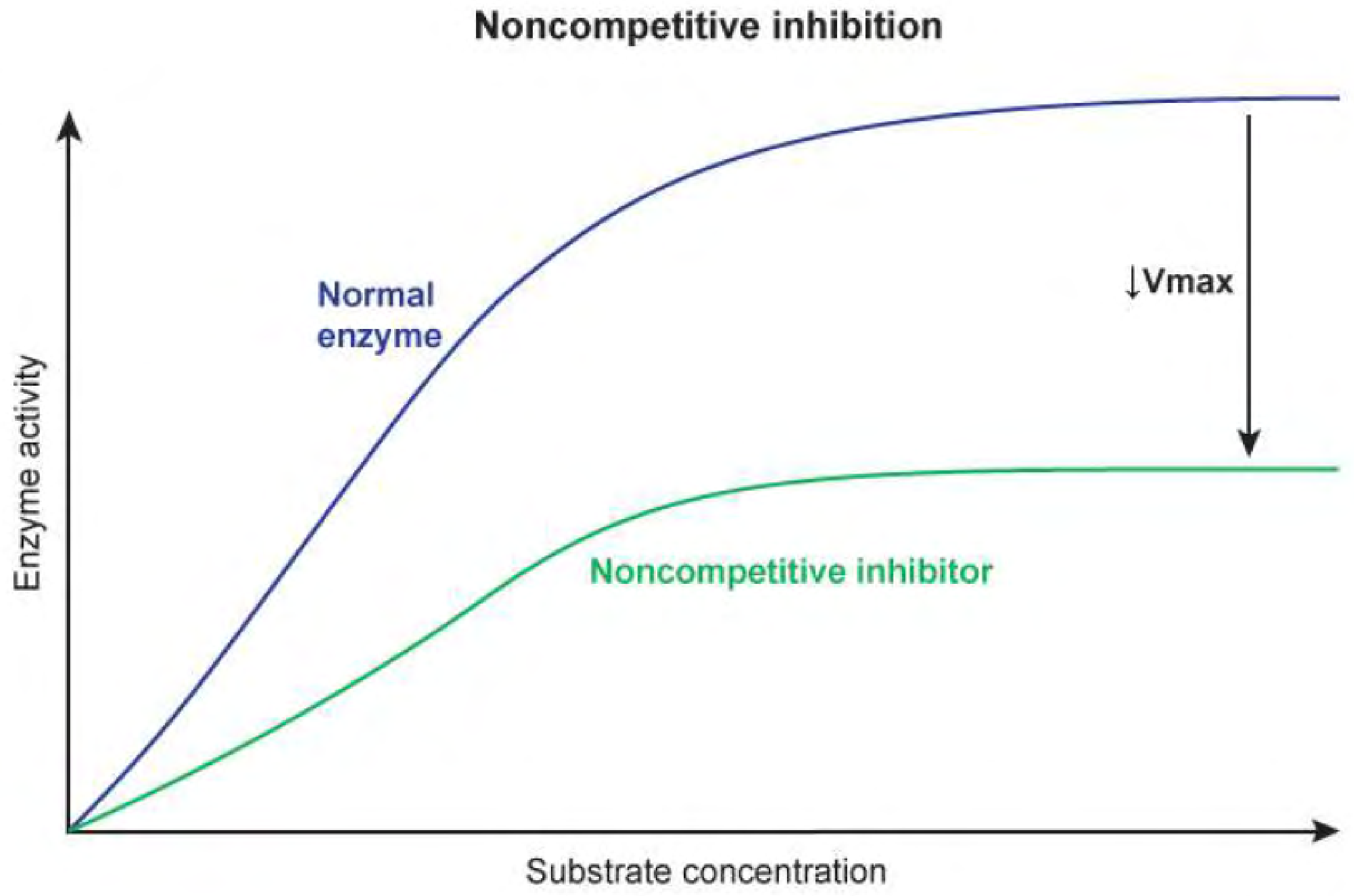

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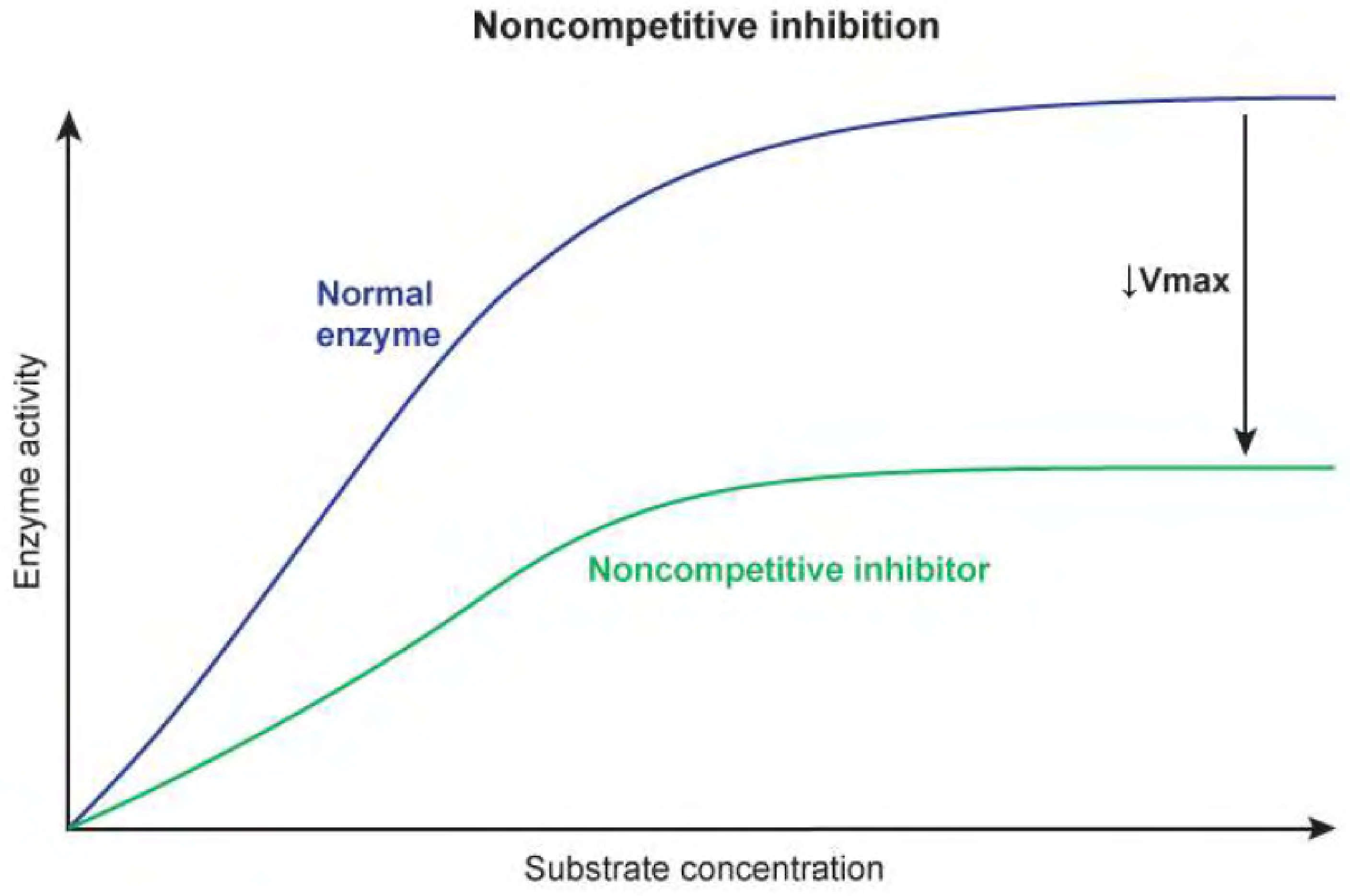

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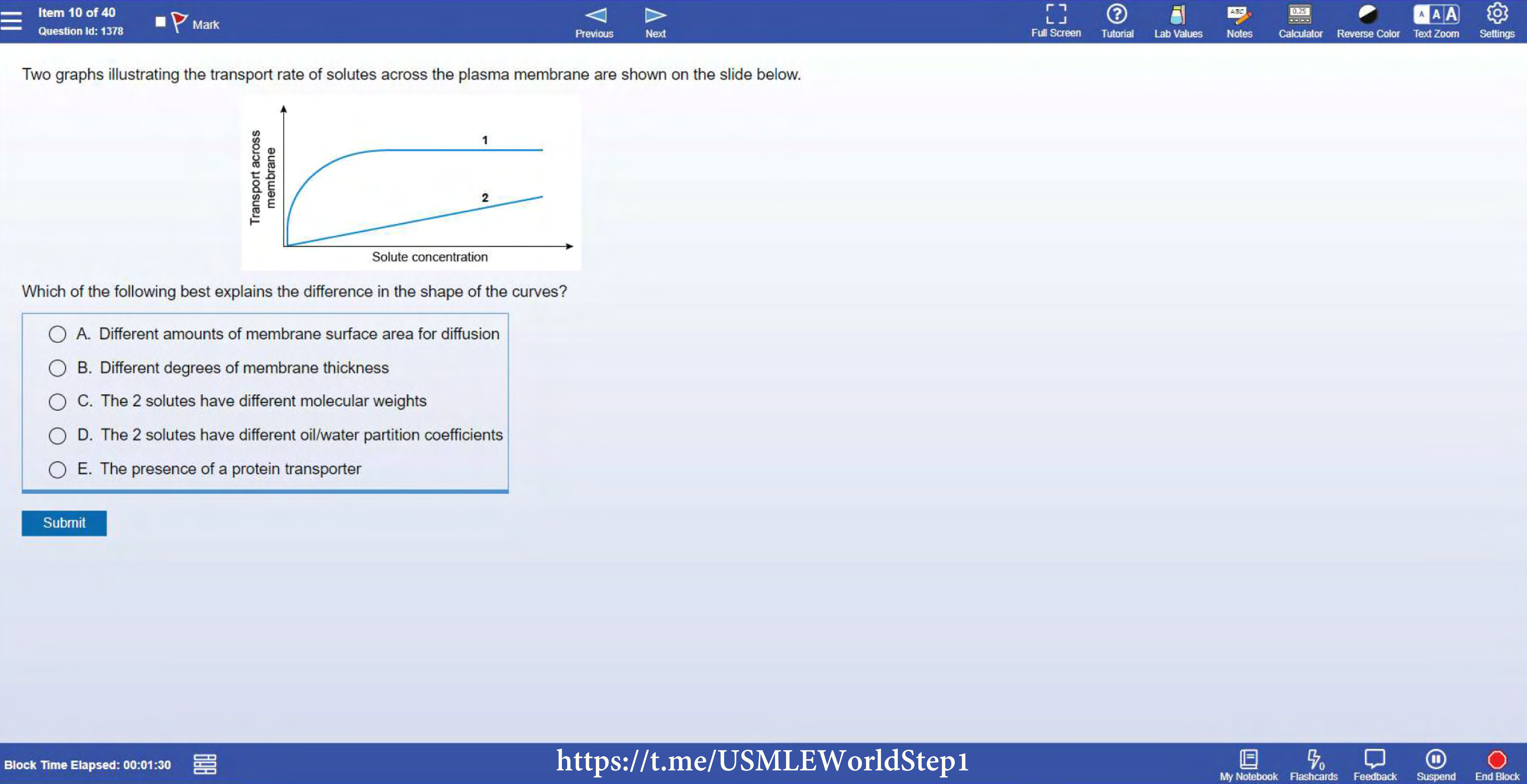

Item 10 of 40
Question Id: 1378
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Transport across membrane
1
2
Solute concentration
Block Time Elapsed: 00:01:30
My Notebook
Flashcards
Feedback
Suspend
End Block

Two graphs illustrating the transport rate of solutes across the plasma membrane are shown on the slide below.

Which of the following best explains the difference in the shape of the curves?

- ○ A. Different amounts of membrane surface area for diffusion
- ○ B. Different degrees of membrane thickness
- ○ C. The 2 solutes have different molecular weights
- ○ D. The 2 solutes have different oil/water partition coefficients
- ○ E. The presence of a protein transporter

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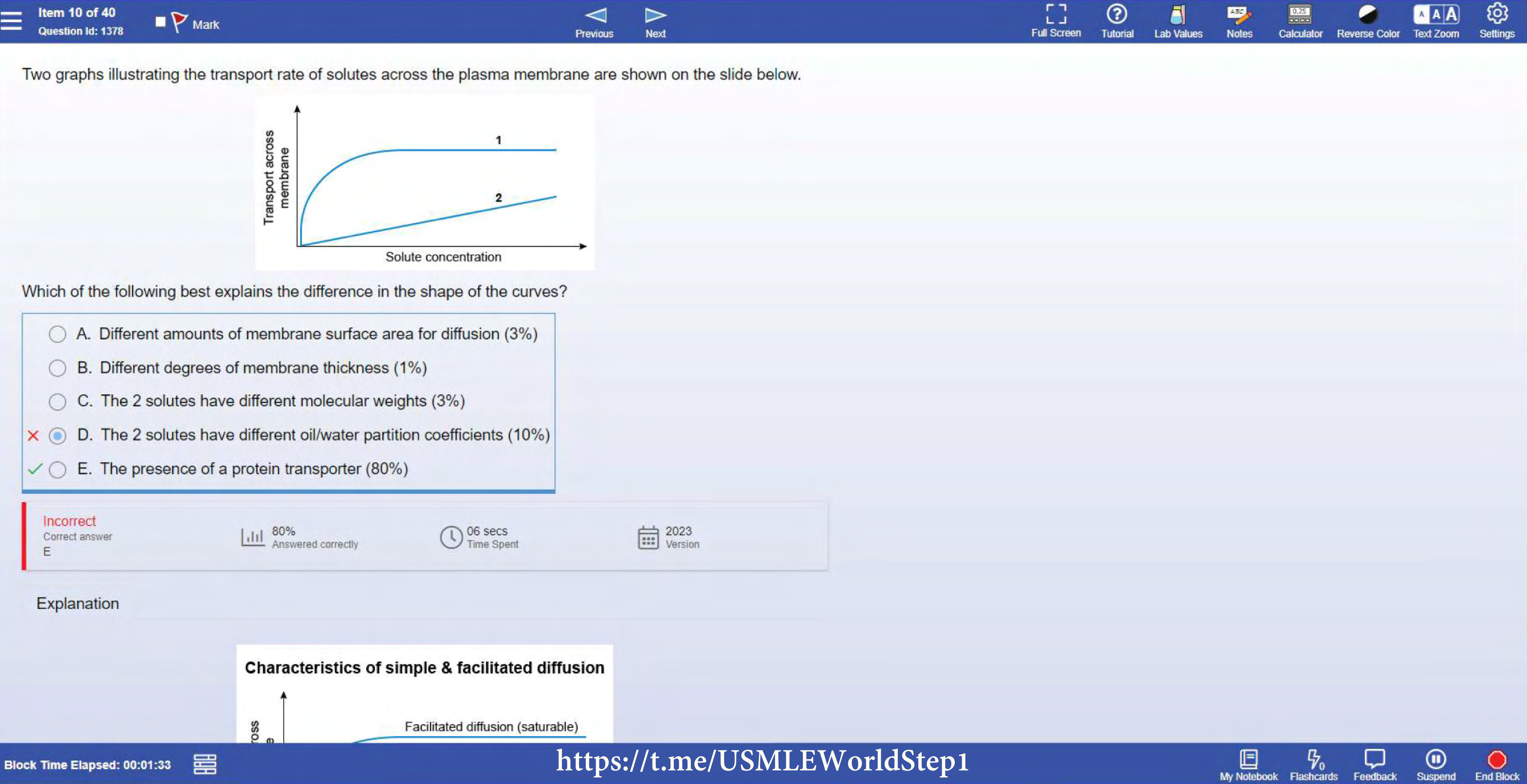
Item 10 of 40
Question Id: 1378
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Two graphs illustrating the transport rate of solutes across the plasma membrane are shown on the slide below.

Transport across membrane
1
2
Solute concentration

Which of the following best explains the difference in the shape of the curves?

○ A. Different amounts of membrane surface area for diffusion (3%)

○ B. Different degrees of membrane thickness (1%)

○ C. The 2 solutes have different molecular weights (3%)

✗ ● D. The 2 solutes have different oil/water partition coefficients (10%)

✓ ○ E. The presence of a protein transporter (80%)

Incorrect
Correct answer
E

80%
Answered correctly

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Time Spent

2023
Version

Explanation

Characteristics of simple & facilitated diffusion

Facilitated diffusion (saturable)
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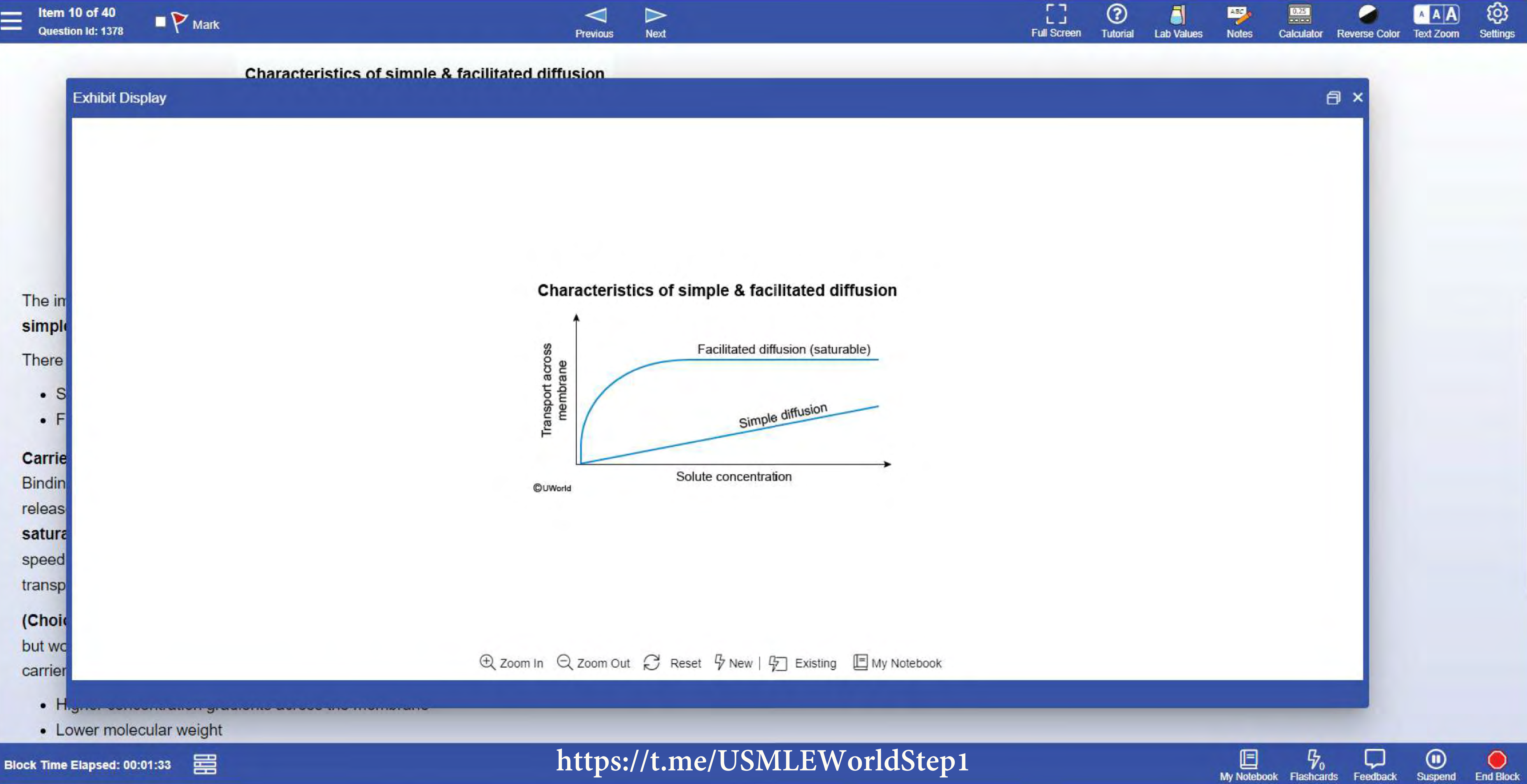
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 10 of 40
Question Id: 1378
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Characteristics of simple & facilitated diffusion
Transport across membrane
Facilitated diffusion (saturable)
Simple diffusion
Solute concentration
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Zoom In
Zoom Out
Reset
New
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My Notebook
Block Time Elapsed: 00:01:33
My Notebook
Flashcards
Feedback
Suspend
End Block

Characteristics of simple & facilitated diffusion

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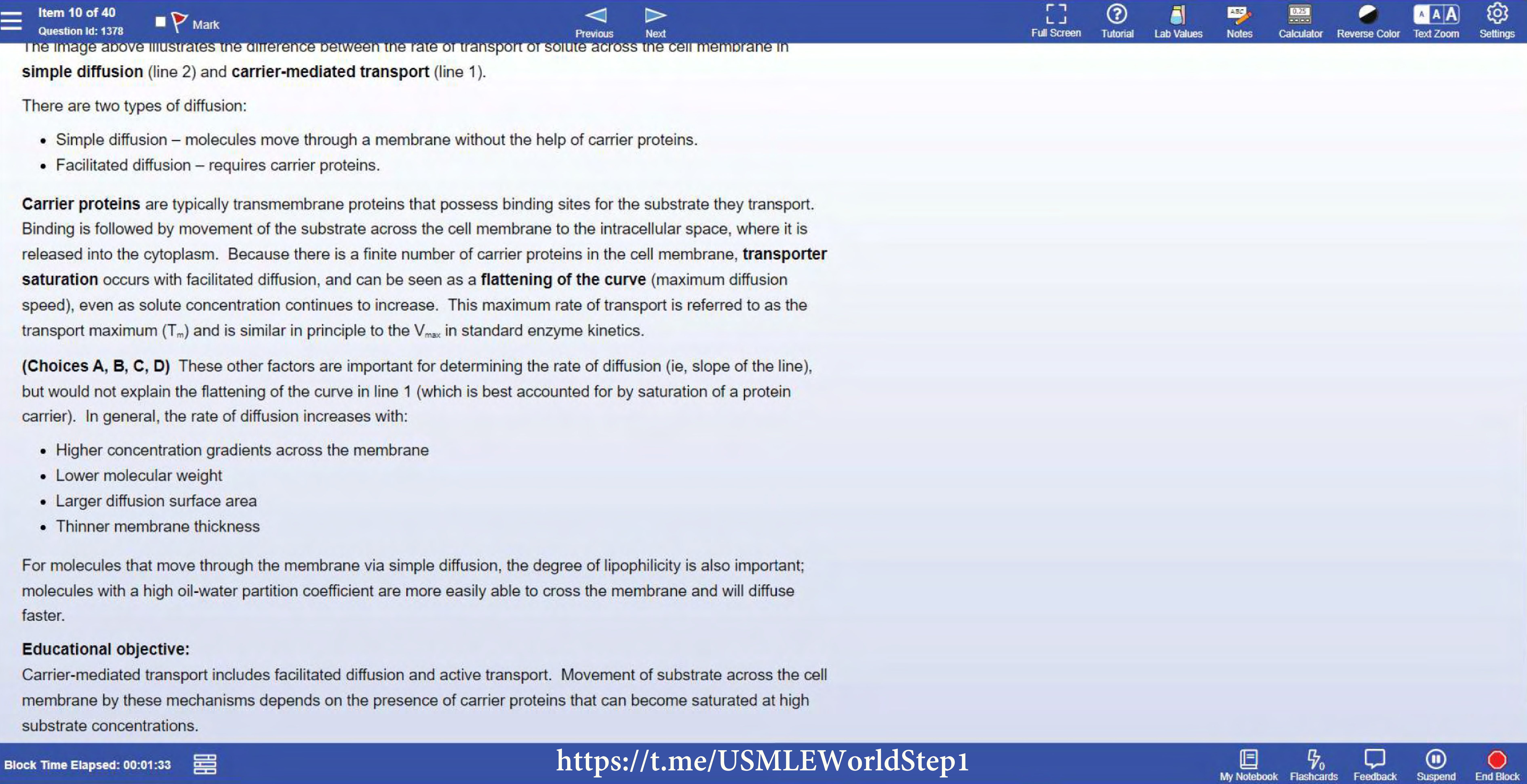


The image above illustrates the difference between the rate of transport of solute across the cell membrane in **simple diffusion** (line 2) and **carrier-mediated transport** (line 1).

There are two types of diffusion:

- Simple diffusion – molecules move through a membrane without the help of carrier proteins.
- Facilitated diffusion – requires carrier proteins.

Carrier proteins are typically transmembrane proteins that possess binding sites for the substrate they transport. Binding is followed by movement of the substrate across the cell membrane to the intracellular space, where it is released into the cytoplasm. Because there is a finite number of carrier proteins in the cell membrane, **transporter saturation** occurs with facilitated diffusion, and can be seen as a **flattening of the curve** (maximum diffusion speed), even as solute concentration continues to increase. This maximum rate of transport is referred to as the transport maximum (T_m) and is similar in principle to the V_{max} in standard enzyme kinetics.

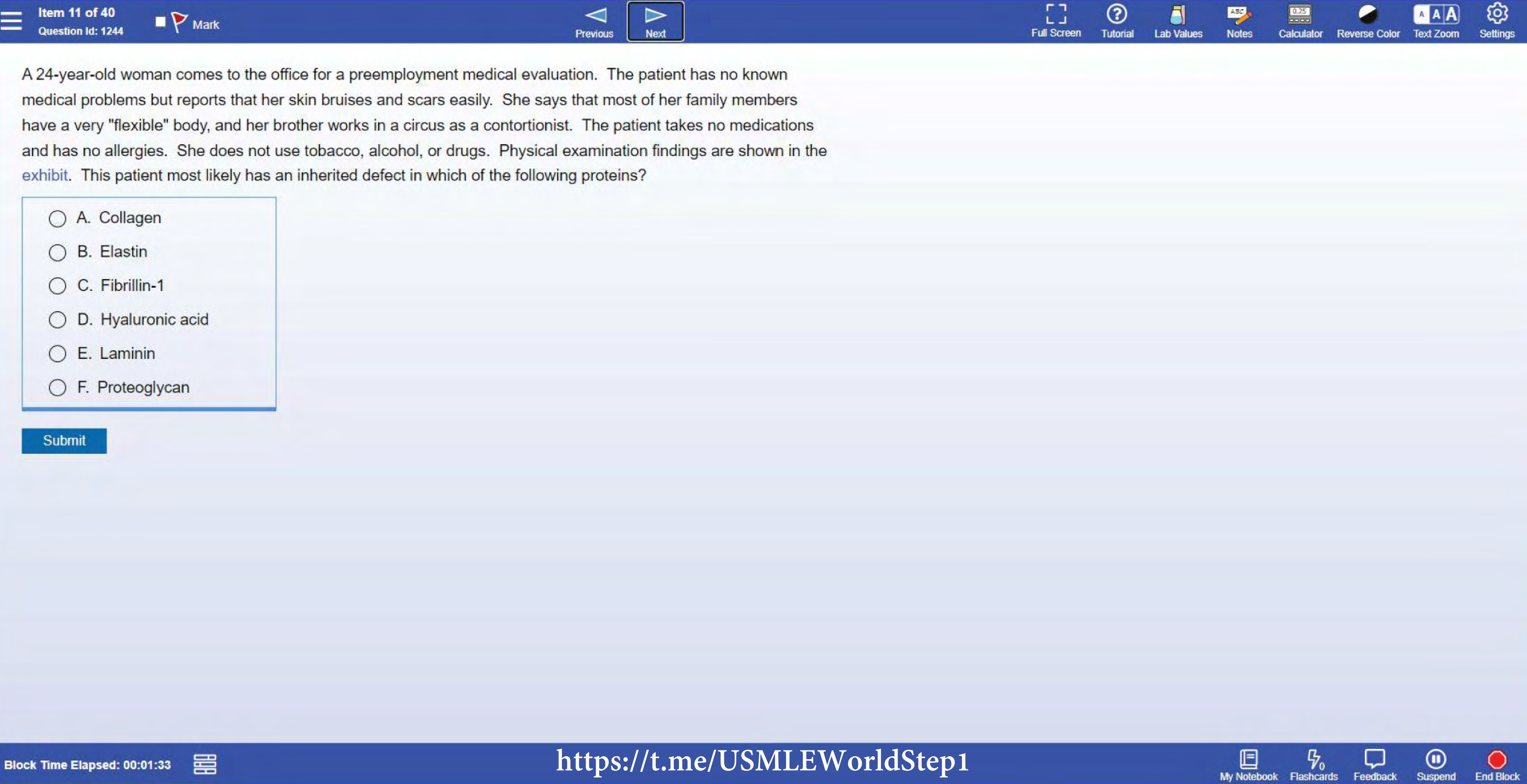
(Choices A, B, C, D) These other factors are important for determining the rate of diffusion (ie, slope of the line), but would not explain the flattening of the curve in line 1 (which is best accounted for by saturation of a protein carrier). In general, the rate of diffusion increases with:

- Higher concentration gradients across the membrane
- Lower molecular weight
- Larger diffusion surface area
- Thinner membrane thickness

For molecules that move through the membrane via simple diffusion, the degree of lipophilicity is also important; molecules with a high oil-water partition coefficient are more easily able to cross the membrane and will diffuse faster.

Educational objective:

Carrier-mediated transport includes facilitated diffusion and active transport. Movement of substrate across the cell membrane by these mechanisms depends on the presence of carrier proteins that can become saturated at high substrate concentrations.


Item 11 of 40
Question Id: 1244
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 24-year-old woman comes to the office for a preemployment medical evaluation. The patient has no known medical problems but reports that her skin bruises and scars easily. She says that most of her family members have a very "flexible" body, and her brother works in a circus as a contortionist. The patient takes no medications and has no allergies. She does not use tobacco, alcohol, or drugs. Physical examination findings are shown in the exhibit. This patient most likely has an inherited defect in which of the following proteins?

○ A. Collagen
○ B. Elastin
○ C. Fibrillin-1
○ D. Hyaluronic acid
○ E. Laminin
○ F. Proteoglycan

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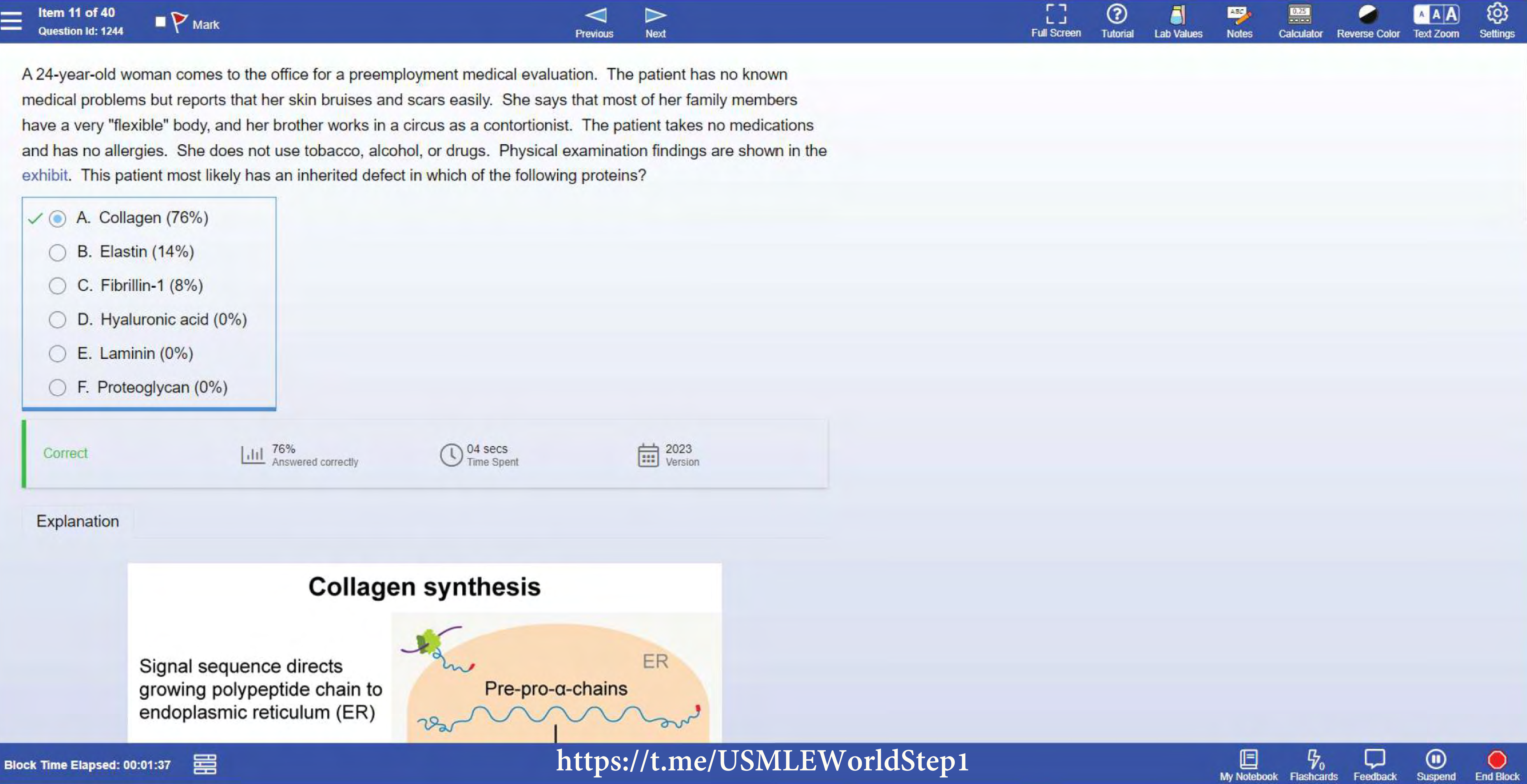
Block Time Elapsed: 00:01:33
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 11 of 40
Question Id: 1244
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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✓ ● A. Collagen (76%)
○ B. Elastin (14%)
○ C. Fibrillin-1 (8%)
○ D. Hyaluronic acid (0%)
○ E. Laminin (0%)
○ F. Proteoglycan (0%)

Correct

76%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Collagen synthesis

Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)

ER
Pre-pro-α-chains

Block Time Elapsed: 00:01:37
My Notebook
Flashcards
Feedback
Suspend
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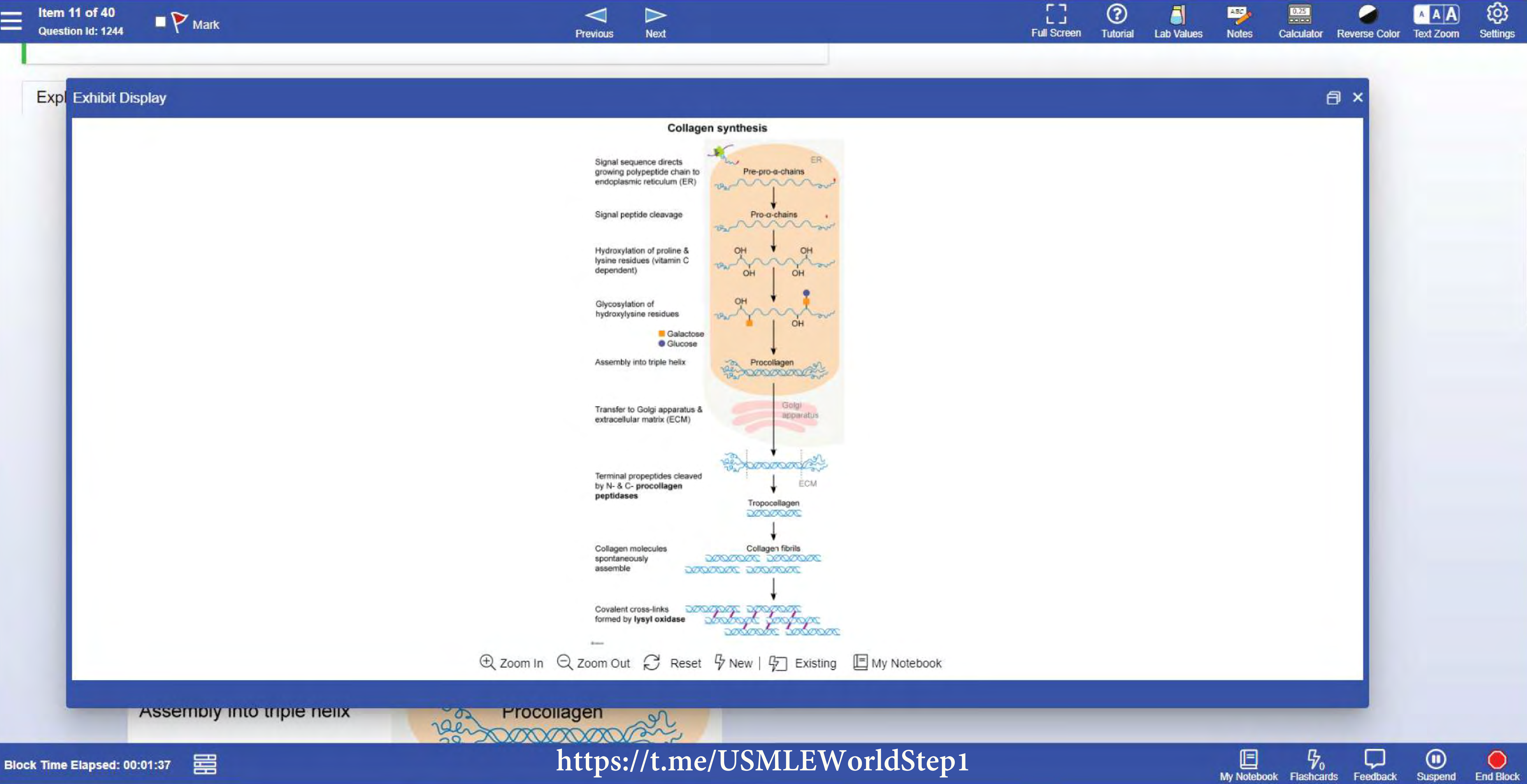
Item 11 of 40
Question Id: 1244
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
ER
Pre-pro-α-chains
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Procollagen
Golgi apparatus
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Collagen fibrils
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Assembly into triple helix
Procollagen
Block Time Elapsed: 00:01:37
My Notebook
Flashcards
Feedback
Suspend
End Block

Collagen synthesis

Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)

Signal peptide cleavage

Hydroxylation of proline & lysine residues (vitamin C dependent)

Glycosylation of hydroxylysine residues

🟧 Galactose
● Glucose

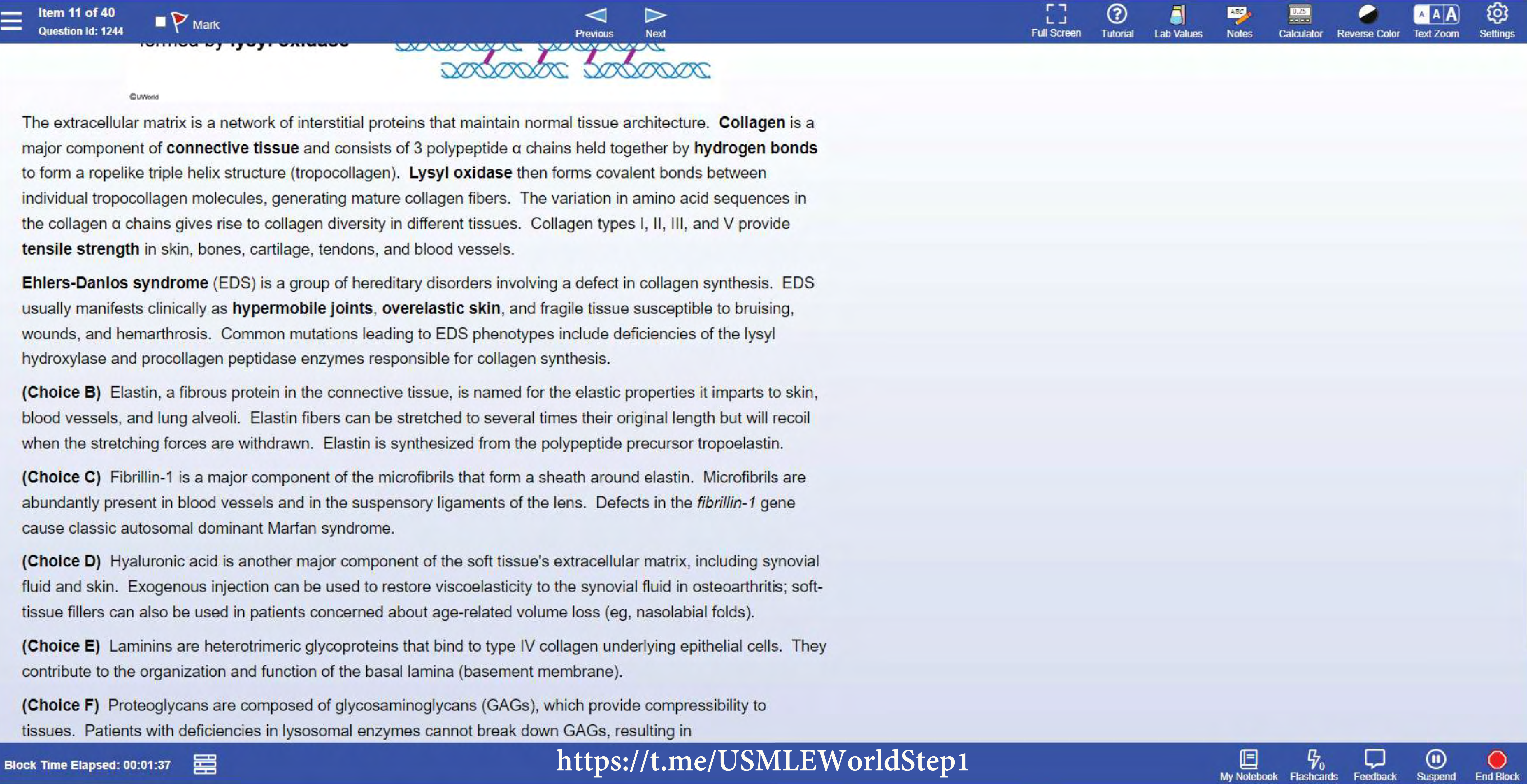
Assembly into triple helix

Transfer to Golgi apparatus & extracellular matrix (ECM)

Terminal propeptides cleaved by N- & C- **procollagen peptidases**

Collagen molecules spontaneously assemble

Covalent cross-links formed by **lysyl oxidase**



The extracellular matrix is a network of interstitial proteins that maintain normal tissue architecture. **Collagen** is a major component of **connective tissue** and consists of 3 polypeptide α chains held together by **hydrogen bonds** to form a ropelike triple helix structure (tropocollagen). **Lysyl oxidase** then forms covalent bonds between individual tropocollagen molecules, generating mature collagen fibers. The variation in amino acid sequences in the collagen α chains gives rise to collagen diversity in different tissues. Collagen types I, II, III, and V provide **tensile strength** in skin, bones, cartilage, tendons, and blood vessels.

Ehlers-Danlos syndrome (EDS) is a group of hereditary disorders involving a defect in collagen synthesis. EDS usually manifests clinically as **hypermobile joints**, **overelastic skin**, and fragile tissue susceptible to bruising, wounds, and hemarthrosis. Common mutations leading to EDS phenotypes include deficiencies of the lysyl hydroxylase and procollagen peptidase enzymes responsible for collagen synthesis.

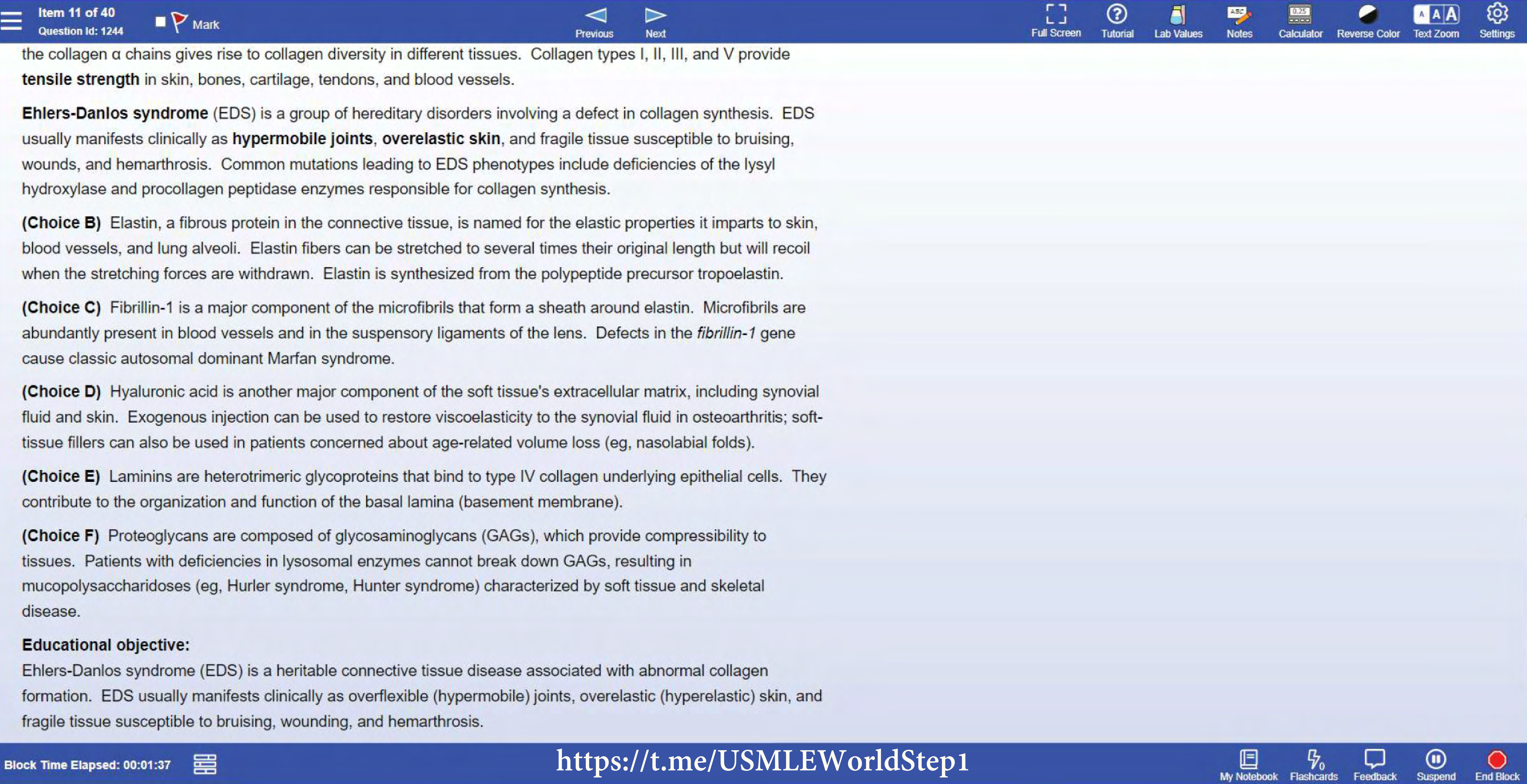
(Choice B) Elastin, a fibrous protein in the connective tissue, is named for the elastic properties it imparts to skin, blood vessels, and lung alveoli. Elastin fibers can be stretched to several times their original length but will recoil when the stretching forces are withdrawn. Elastin is synthesized from the polypeptide precursor tropoelastin.

(Choice C) Fibrillin-1 is a major component of the microfibrils that form a sheath around elastin. Microfibrils are abundantly present in blood vessels and in the suspensory ligaments of the lens. Defects in the *fibrillin-1* gene cause classic autosomal dominant Marfan syndrome.

(Choice D) Hyaluronic acid is another major component of the soft tissue's extracellular matrix, including synovial fluid and skin. Exogenous injection can be used to restore viscoelasticity to the synovial fluid in osteoarthritis; soft-tissue fillers can also be used in patients concerned about age-related volume loss (eg, nasolabial folds).

(Choice E) Laminins are heterotrimeric glycoproteins that bind to type IV collagen underlying epithelial cells. They contribute to the organization and function of the basal lamina (basement membrane).

(Choice F) Proteoglycans are composed of glycosaminoglycans (GAGs), which provide compressibility to tissues. Patients with deficiencies in lysosomal enzymes cannot break down GAGs, resulting in



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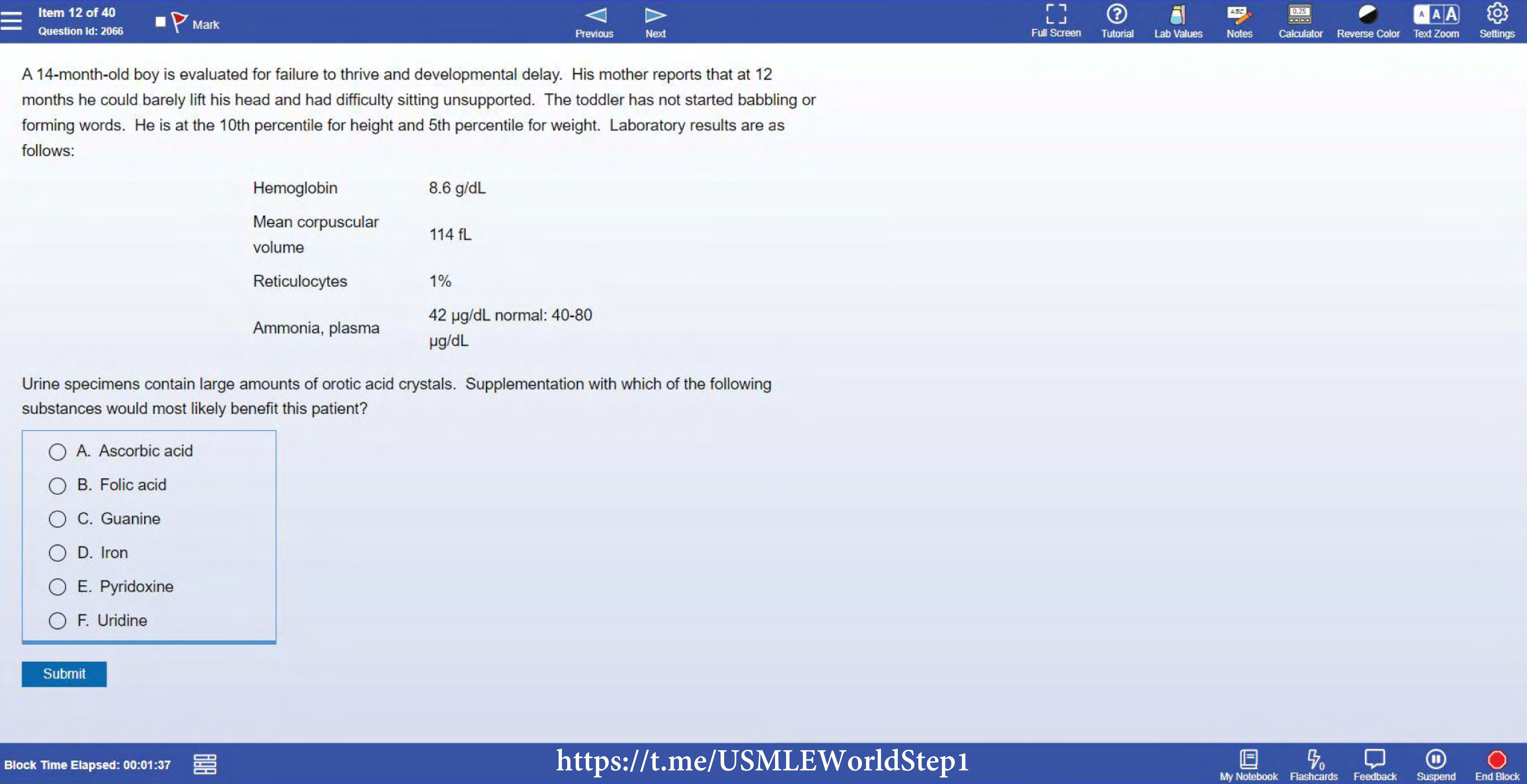
(Choice F) Proteoglycans are composed of glycosaminoglycans (GAGs), which provide compressibility to tissues. Patients with deficiencies in lysosomal enzymes cannot break down GAGs, resulting in mucopolysaccharidoses (eg, Hurler syndrome, Hunter syndrome) characterized by soft tissue and skeletal disease.

Educational objective:

Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disease associated with abnormal collagen formation. EDS usually manifests clinically as overflexible (hypermobile) joints, overelastic (hyperelastic) skin, and fragile tissue susceptible to bruising, wounding, and hemarthrosis.


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 12 of 40
Question Id: 2066

A 14-month-old boy is evaluated for failure to thrive and developmental delay. His mother reports that at 12 months he could barely lift his head and had difficulty sitting unsupported. The toddler has not started babbling or forming words. He is at the 10th percentile for height and 5th percentile for weight. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

- ○ A. Ascorbic acid
- ○ B. Folic acid
- ○ C. Guanine
- ○ D. Iron
- ○ E. Pyridoxine
- ○ F. Uridine

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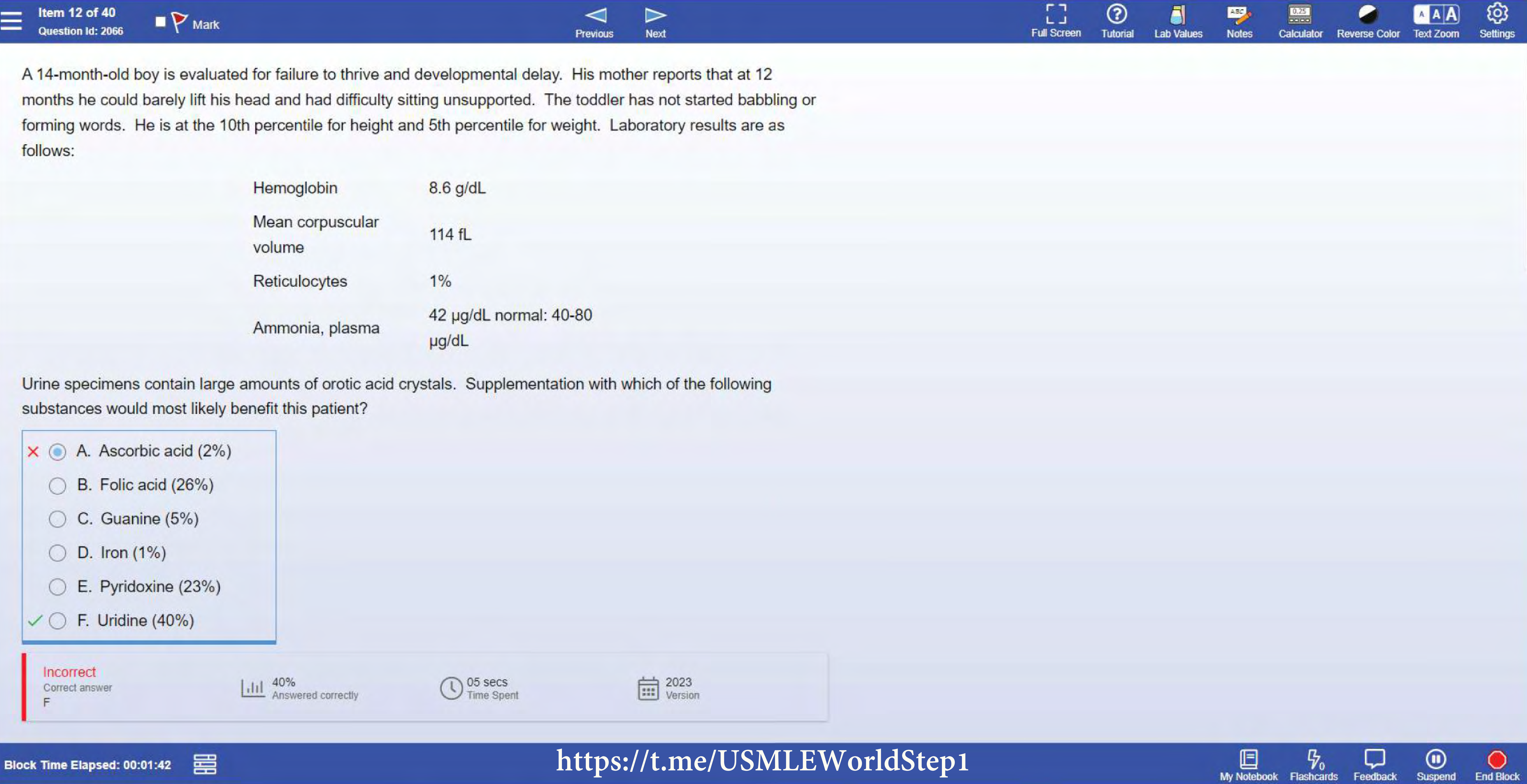
Item 12 of 40
Question Id: 2066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

- ✗ ● A. Ascorbic acid (2%)
- ○ B. Folic acid (26%)
- ○ C. Guanine (5%)
- ○ D. Iron (1%)
- ○ E. Pyridoxine (23%)
- ✓ ○ F. Uridine (40%)

Incorrect Correct answer F	40% Answered correctly	05 secs Time Spent	2023 Version

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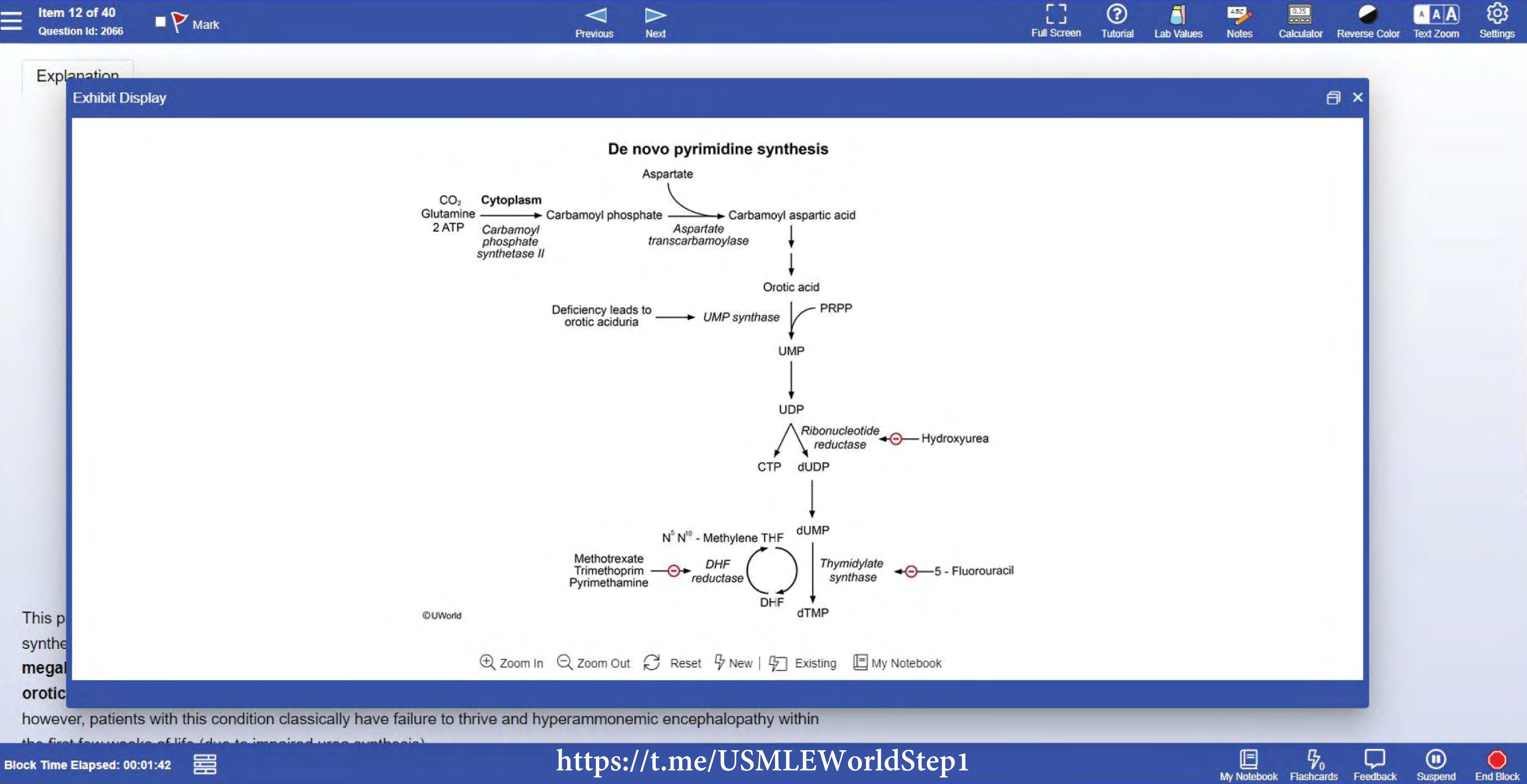
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 12 of 40
Question Id: 2066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
De novo pyrimidine synthesis
Aspartate
CO₂
Glutamine
2 ATP
Cytoplasm
Carbamoyl phosphate
Carbamoyl phosphate synthetase II
Aspartate transcarbamoylase
Carbamoyl aspartic acid
Orotic acid
Deficiency leads to orotic aciduria
UMP synthase
PRPP
UMP
UDP
Ribonucleotide reductase
Hydroxyurea
CTP
dUDP
dUMP
N⁵ N¹⁰ - Methylene THF
Methotrexate
Trimethoprim
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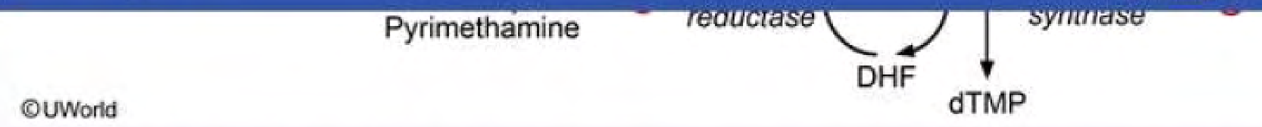
however, patients with this condition classically have failure to thrive and hyperammonemic encephalopathy within



This patient likely has **hereditary orotic aciduria**, a rare autosomal recessive disorder of de novo pyrimidine synthesis that results in **developmental delay** (eg, low height/weight, absent developmental milestones), **megaloblastic anemia** (eg, elevated mean corpuscular volume, low reticulocyte count), and **elevated urinary orotic acid** levels. Increased urinary orotic acid may also be seen in ornithine transcarbamylase deficiency; however, patients with this condition classically have failure to thrive and hyperammonemic encephalopathy within the first few weeks of life (due to impaired urea synthesis).

Hereditary orotic aciduria occurs due to a **defect** in **uridine 5'-monophosphate (UMP) synthase**, a polypeptide containing 2 enzymatic domains (orotate phosphoribosyltransferase and OMP decarboxylase) that catalyze the final conversion of orotic acid to UMP. Impaired conversion of orotic acid to UMP results in the excretion of large amounts of orotic acid in the urine and the clinical features described above. **Uridine supplementation** can bypass this enzymatic defect and improve symptoms as uridine is converted to UMP via nucleoside kinases.

(Choice A) Ascorbic acid (vitamin C) is required for hydroxylation of proline and lysine residues in collagen synthesis; therefore, it plays an important role in connective tissue maintenance and wound healing.

(Choice B) Folate participates in single carbon transfer reactions, as in the de novo synthesis of purines and thymidine. Folate supplements will improve megaloblastic anemia resulting from folate deficiency but will not improve the anemia in orotic aciduria.

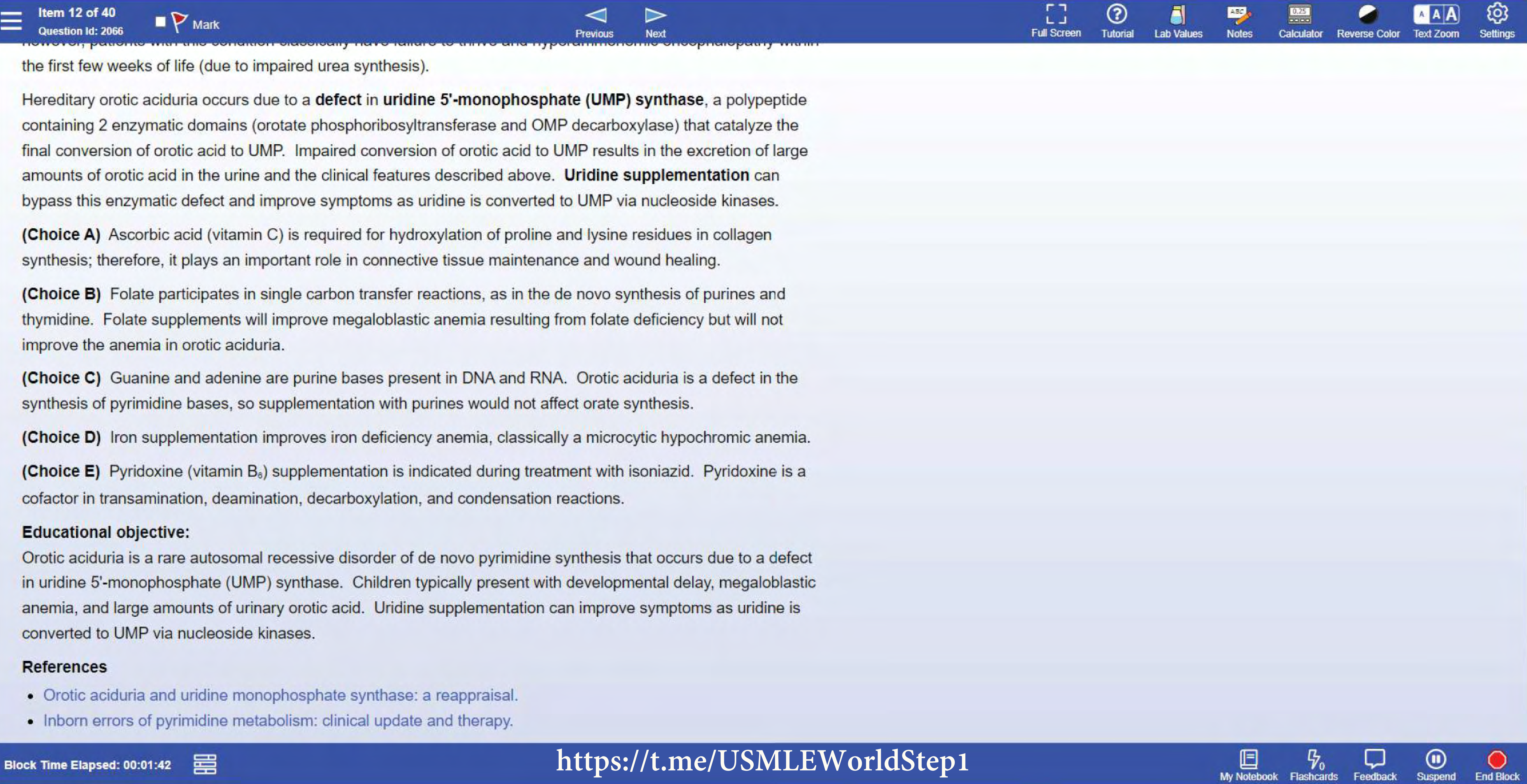
(Choice C) Guanine and adenine are purine bases present in DNA and RNA. Orotic aciduria is a defect in the synthesis of pyrimidine bases, so supplementation with purines would not affect orate synthesis.

(Choice D) Iron supplementation improves iron deficiency anemia, classically a microcytic hypochromic anemia.

(Choice E) Pyridoxine (vitamin B_6) supplementation is indicated during treatment with isoniazid. Pyridoxine is a cofactor in transamination, deamination, decarboxylation, and condensation reactions.

Educational objective:

Orotic aciduria is a rare autosomal recessive disorder of de novo pyrimidine synthesis that occurs due to a defect



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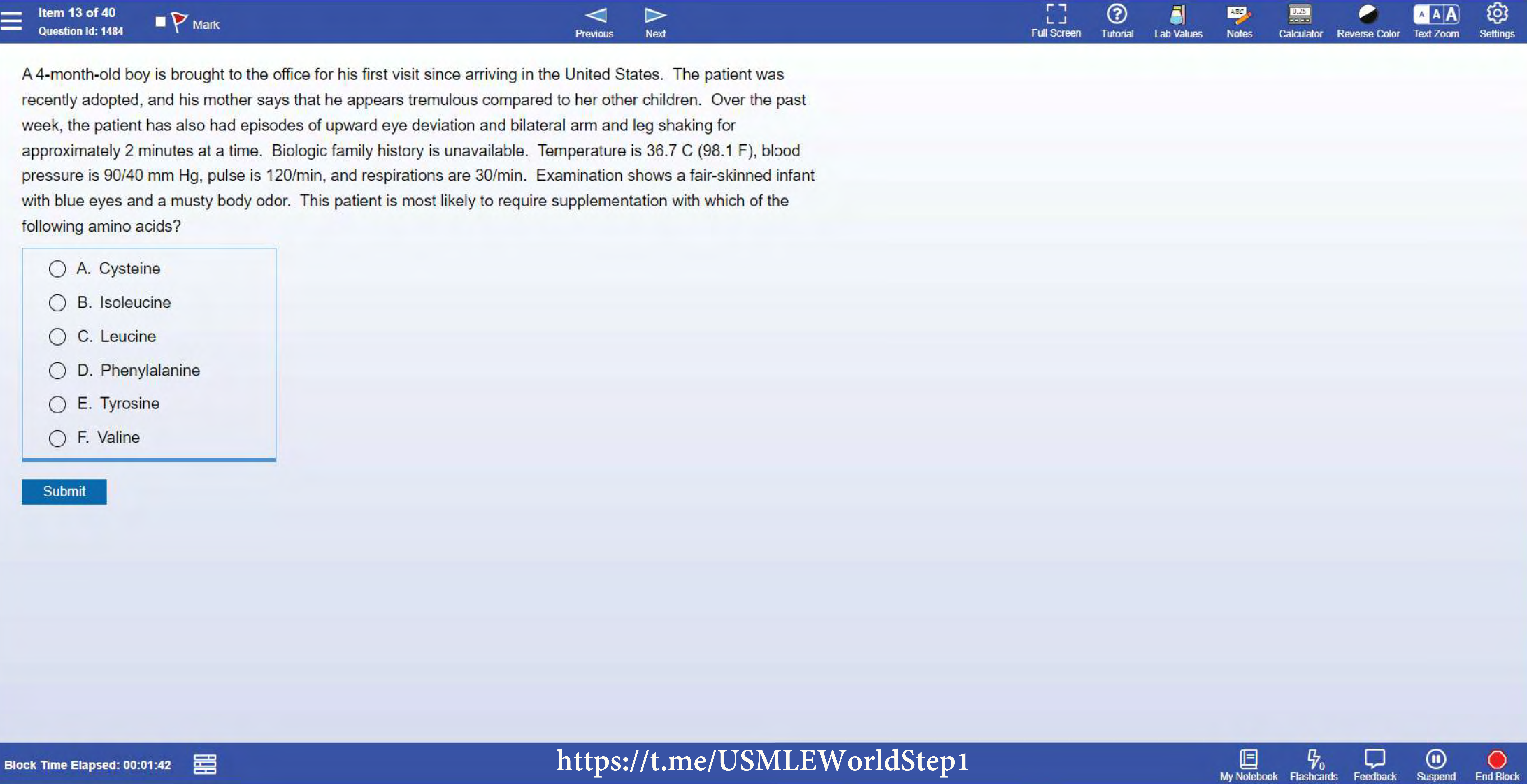
Educational objective:

Orotic aciduria is a rare autosomal recessive disorder of de novo pyrimidine synthesis that occurs due to a defect in uridine 5'-monophosphate (UMP) synthase. Children typically present with developmental delay, megaloblastic anemia, and large amounts of urinary orotic acid. Uridine supplementation can improve symptoms as uridine is converted to UMP via nucleoside kinases.

References

- Orotic aciduria and uridine monophosphate synthase: a reappraisal.
- Inborn errors of pyrimidine metabolism: clinical update and therapy.


Item 13 of 40
Question Id: 1484
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 4-month-old boy is brought to the office for his first visit since arriving in the United States. The patient was recently adopted, and his mother says that he appears tremulous compared to her other children. Over the past week, the patient has also had episodes of upward eye deviation and bilateral arm and leg shaking for approximately 2 minutes at a time. Biologic family history is unavailable. Temperature is 36.7 C (98.1 F), blood pressure is 90/40 mm Hg, pulse is 120/min, and respirations are 30/min. Examination shows a fair-skinned infant with blue eyes and a musty body odor. This patient is most likely to require supplementation with which of the following amino acids?

- ○ A. Cysteine
- ○ B. Isoleucine
- ○ C. Leucine
- ○ D. Phenylalanine
- ○ E. Tyrosine
- ○ F. Valine

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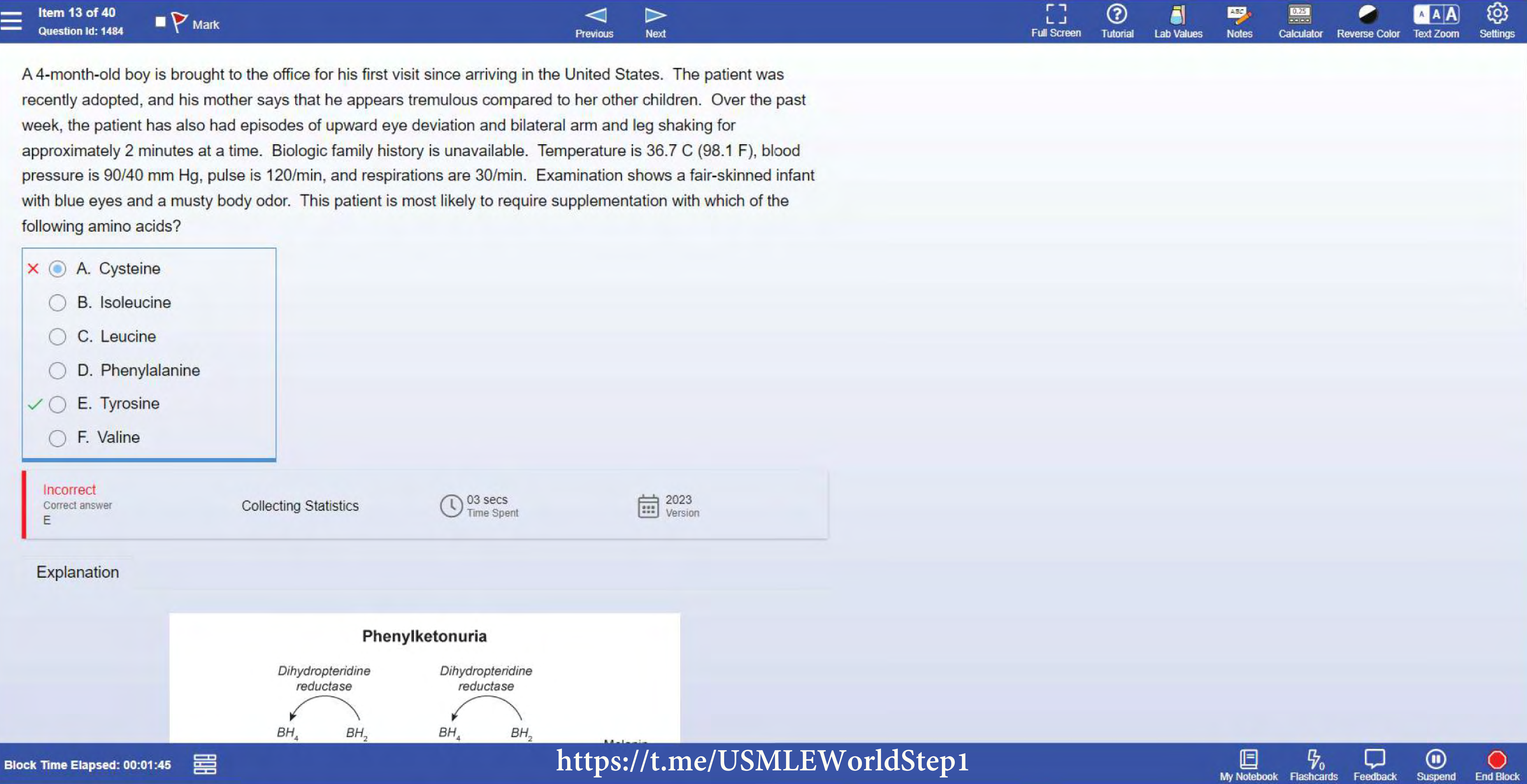
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 13 of 40
Question Id: 1484
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ C. Leucine
- ○ D. Phenylalanine
- ✓ ○ E. Tyrosine
- ○ F. Valine

Incorrect
Correct answer
E

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2023
Version

Explanation

Phenylketonuria

Dihydropteridine reductase
BH_4
BH_2
Dihydropteridine reductase
BH_4
BH_2
Block Time Elapsed: 00:01:45
My Notebook
Flashcards
Feedback
Suspend
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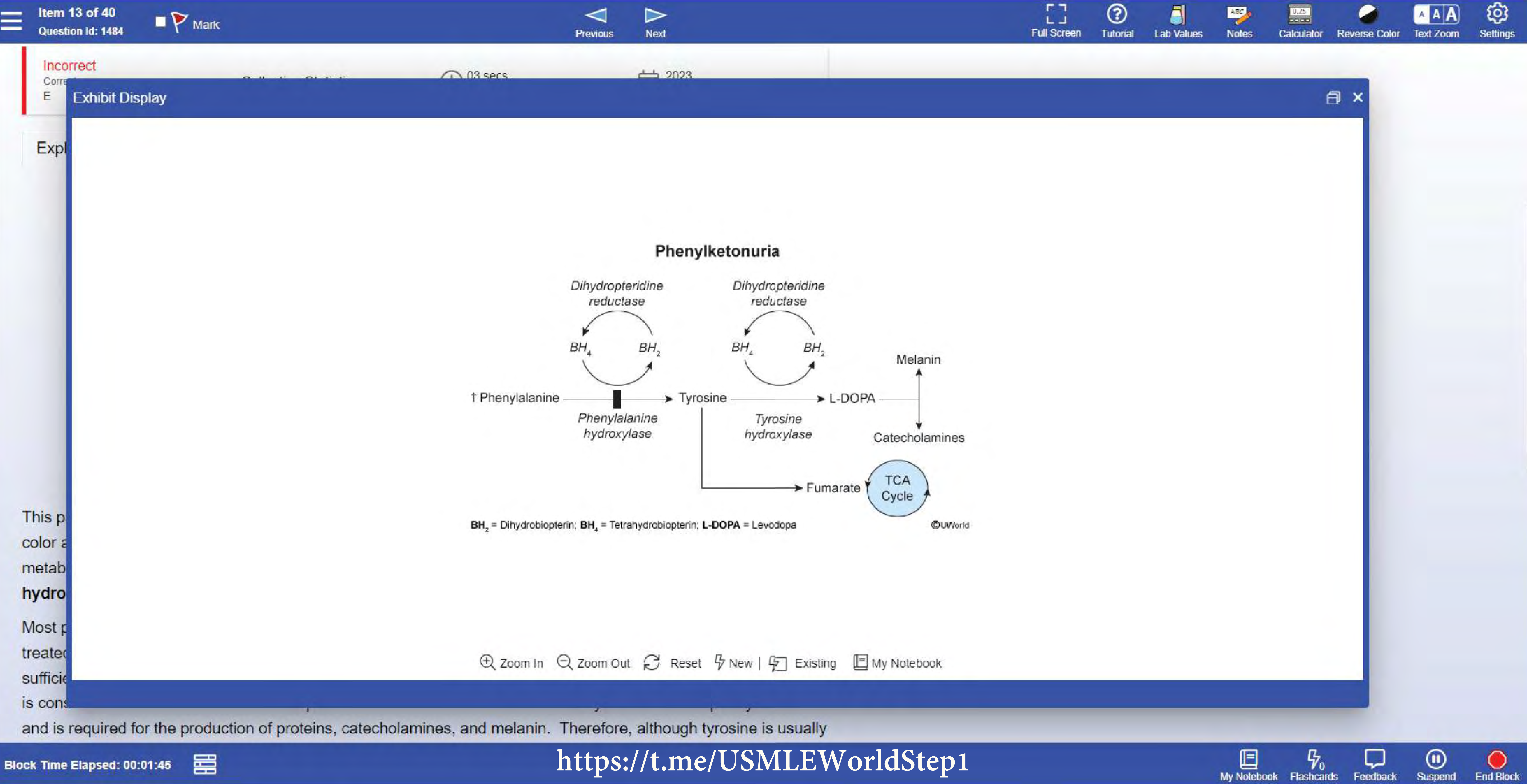
Item 13 of 40
Question Id: 1484
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Expl

Phenylketonuria

Dihydropteridine reductase
BH_4
BH_2
Dihydropteridine reductase
BH_4
BH_2
Melanin
↑ Phenylalanine
Tyrosine
L-DOPA
Phenylalanine hydroxylase
Tyrosine hydroxylase
Catecholamines
Fumarate
TCA Cycle

BH_2 = Dihydrobiopterin; **BH_4** = Tetrahydrobiopterin; **L-DOPA** = Levodopa

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and is required for the production of proteins, catecholamines, and melanin. Therefore, although tyrosine is usually

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My Notebook
Flashcards
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Item 13 of 40
Question Id: 1484
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:01:45
My Notebook
Flashcards
Feedback
Suspend
End Block

BH_2 = Dihydrobiopterin; **BH_4** = Tetrahydrobiopterin; **L-DOPA** = Levodopa ©UWorld

This patient's neurologic abnormalities (eg, tremors, seizures) in the setting of musty body odor and light skin/eye color are suggestive of **phenylketonuria** (PKU), an autosomal recessive disease in which patients have impaired metabolism of phenylalanine, an essential amino acid. PKU is caused by deficiency of **phenylalanine hydroxylase**, which catalyzes the conversion of phenylalanine to tyrosine.

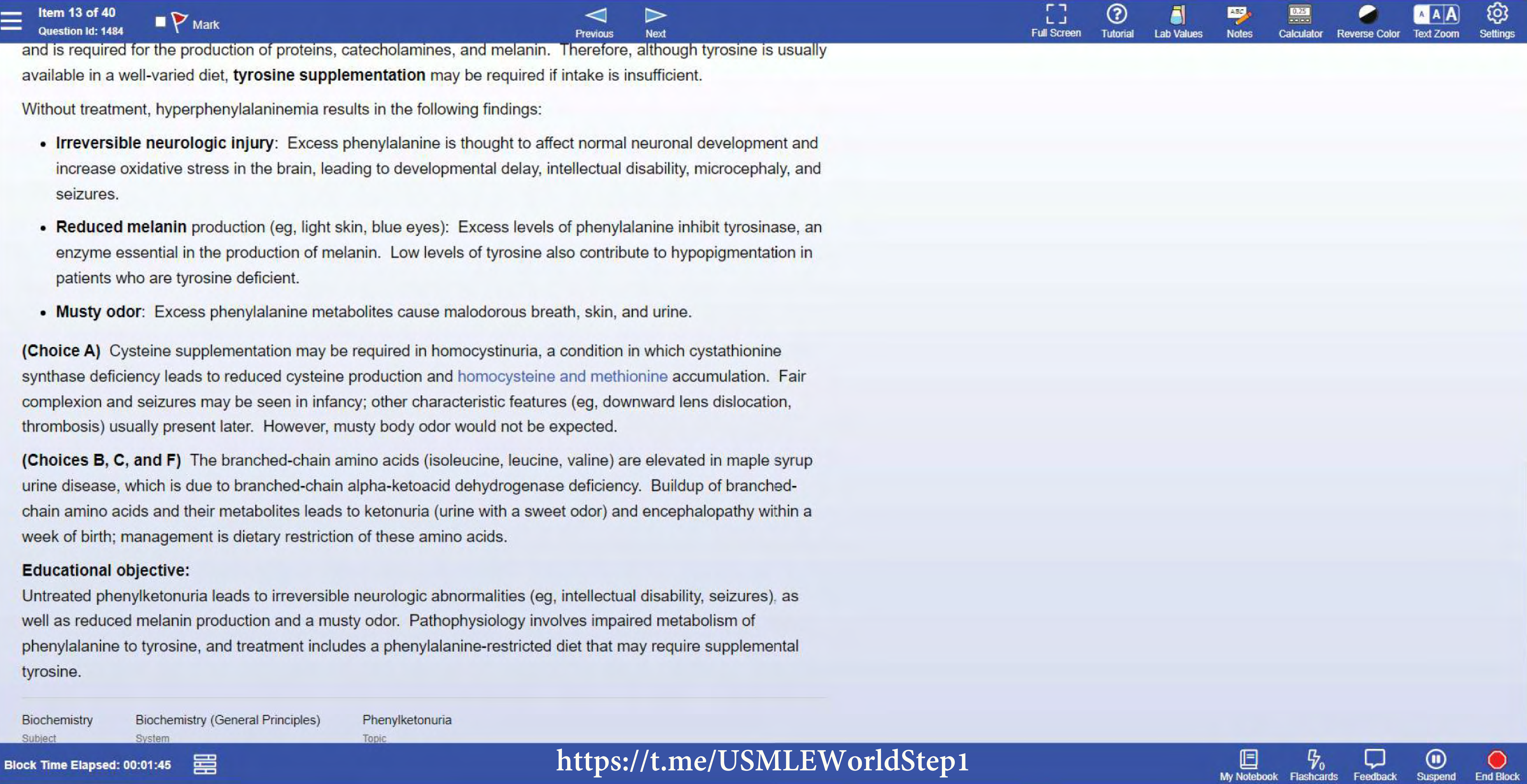
Most patients with PKU are identified via routine newborn screening (ie, via elevated phenylalanine levels) and treated with a **phenylalanine-restricted diet** starting in the neonatal period **(Choice D)**. This diet is typically sufficient to prevent manifestations of disease, which are largely due to hyperphenylalaninemia. However, tyrosine is considered an essential amino acid in patients with PKU because it cannot be synthesized from phenylalanine and is required for the production of proteins, catecholamines, and melanin. Therefore, although tyrosine is usually available in a well-varied diet, **tyrosine supplementation** may be required if intake is insufficient.

Without treatment, hyperphenylalaninemia results in the following findings:

- **Irreversible neurologic injury**: Excess phenylalanine is thought to affect normal neuronal development and increase oxidative stress in the brain, leading to developmental delay, intellectual disability, microcephaly, and seizures.
- **Reduced melanin** production (eg, light skin, blue eyes): Excess levels of phenylalanine inhibit tyrosinase, an enzyme essential in the production of melanin. Low levels of tyrosine also contribute to hypopigmentation in patients who are tyrosine deficient.
- **Musty odor**: Excess phenylalanine metabolites cause malodorous breath, skin, and urine.

(Choice A) Cysteine supplementation may be required in homocystinuria, a condition in which cystathionine synthase deficiency leads to reduced cysteine production and homocysteine and methionine accumulation. Fair complexion and seizures may be seen in infancy; other characteristic features (eg, downward lens dislocation, thrombosis) usually present later. However, musty body odor would not be expected.

(Choices B, C, and F) The branched-chain amino acids (isoleucine, leucine, valine) are elevated in maple syrup urine disease, which is due to branched-chain alpha-ketoacid dehydrogenase deficiency. Buildup of branched-



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(Choices B, C, and F) The branched-chain amino acids (isoleucine, leucine, valine) are elevated in maple syrup urine disease, which is due to branched-chain alpha-ketoacid dehydrogenase deficiency. Buildup of branched-chain amino acids and their metabolites leads to ketonuria (urine with a sweet odor) and encephalopathy within a week of birth; management is dietary restriction of these amino acids.

Educational objective:

Untreated phenylketonuria leads to irreversible neurologic abnormalities (eg, intellectual disability, seizures), as well as reduced melanin production and a musty odor. Pathophysiology involves impaired metabolism of phenylalanine to tyrosine, and treatment includes a phenylalanine-restricted diet that may require supplemental tyrosine.

Biochemistry	Biochemistry (General Principles)	Phenylketonuria
Subject	System	Topic

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and is required for the production of proteins, catecholamines, and melanin. Therefore, although tyrosine is usually available in a well-varied diet, **tyrosine supplementation** may be required if intake is insufficient.

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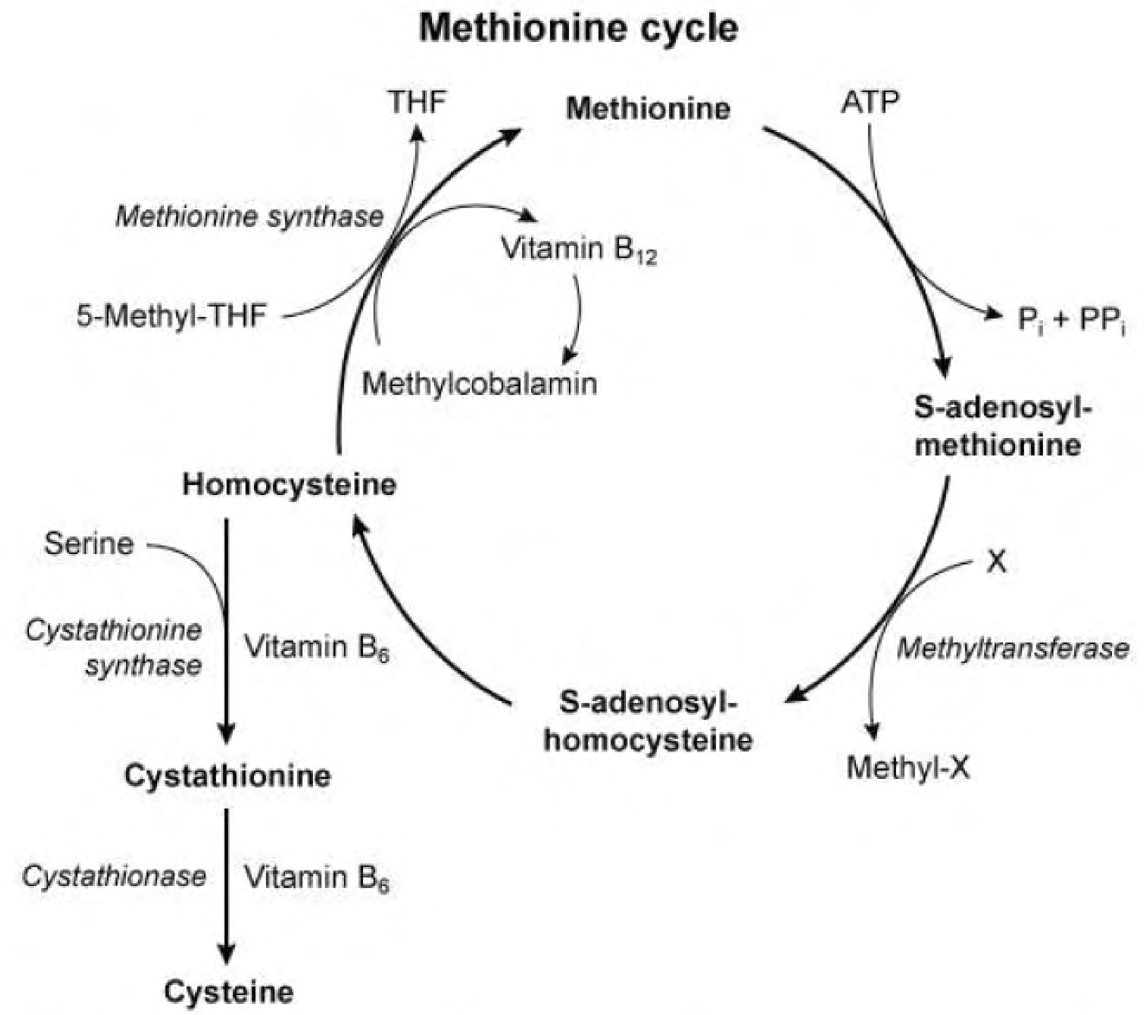
Methionine cycle
THF
Methionine
ATP
Methionine synthase
Vitamin B_{12}
P_i + PP_i
5-Methyl-THF
Methylcobalamin
S-adenosyl-methionine
Homocysteine
X
Serine
Methyltransferase
Cystathionine synthase
Vitamin B_6
S-adenosyl-homocysteine
Methyl-X
Cystathionine
Cystathionase
Vitamin B_6
Cysteine

P_i = inorganic phosphate; **PP_i** = inorganic pyrophosphate (diphosphate);
THF = tetrahydrofolate.

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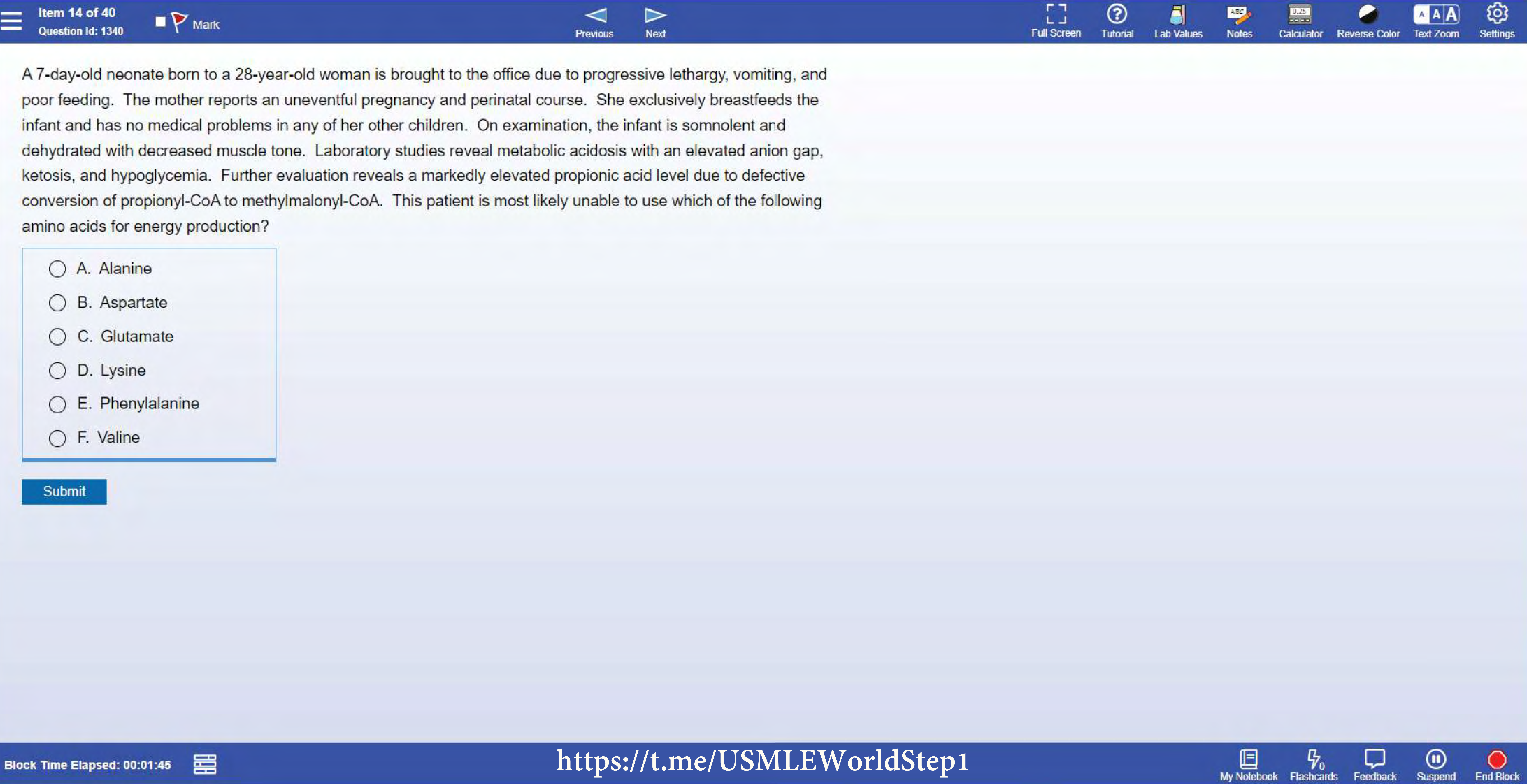
Biochemistry
Subject

Biochemistry (General Principles)
System

Phenylketonuria
Topic


Item 14 of 40
Question Id: 1340
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 7-day-old neonate born to a 28-year-old woman is brought to the office due to progressive lethargy, vomiting, and poor feeding. The mother reports an uneventful pregnancy and perinatal course. She exclusively breastfeeds the infant and has no medical problems in any of her other children. On examination, the infant is somnolent and dehydrated with decreased muscle tone. Laboratory studies reveal metabolic acidosis with an elevated anion gap, ketosis, and hypoglycemia. Further evaluation reveals a markedly elevated propionic acid level due to defective conversion of propionyl-CoA to methylmalonyl-CoA. This patient is most likely unable to use which of the following amino acids for energy production?

- ○ A. Alanine
- ○ B. Aspartate
- ○ C. Glutamate
- ○ D. Lysine
- ○ E. Phenylalanine
- ○ F. Valine

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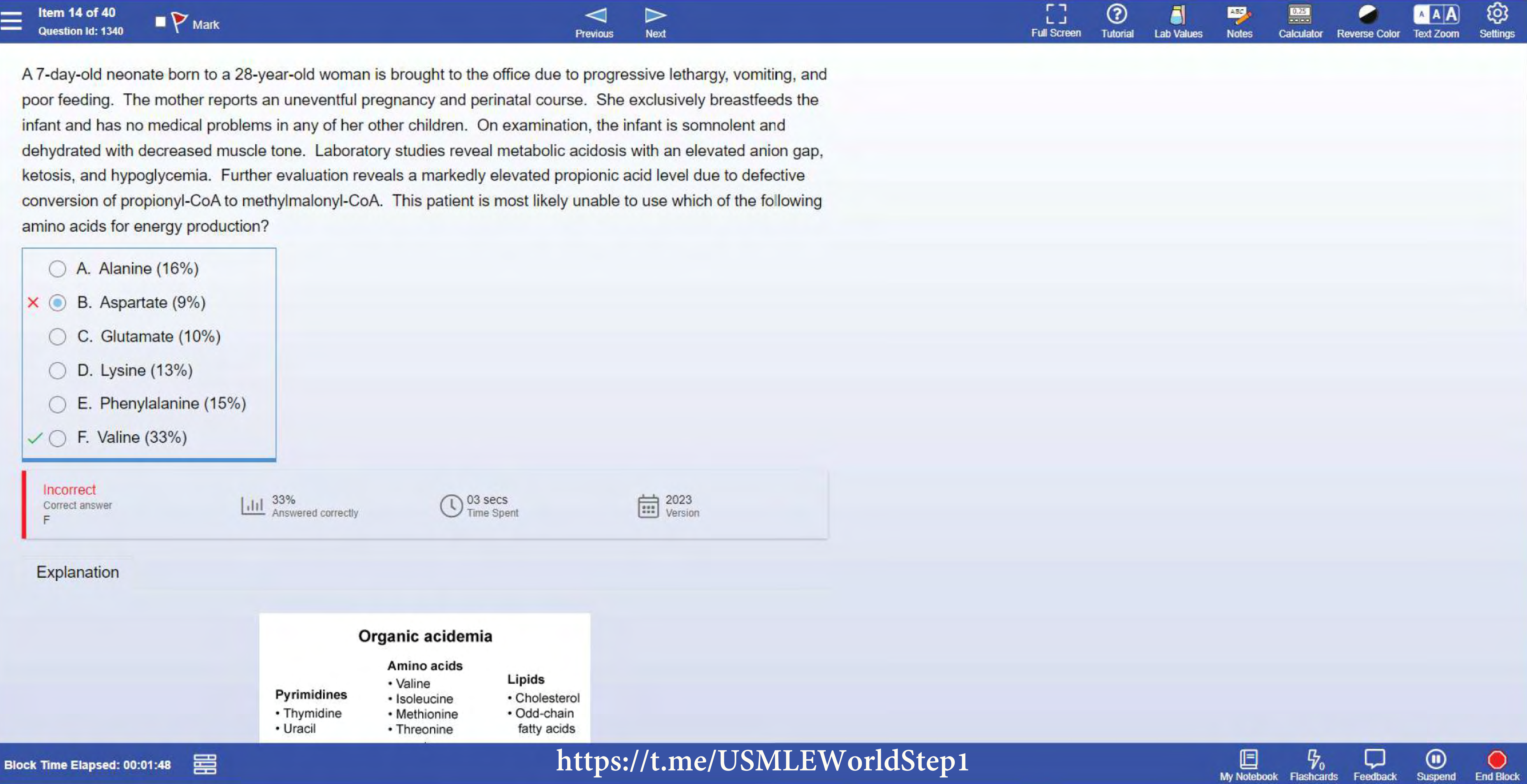
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 14 of 40
Question Id: 1340
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ A. Alanine (16%)
✗ ● B. Aspartate (9%)
○ C. Glutamate (10%)
○ D. Lysine (13%)
○ E. Phenylalanine (15%)
✓ ○ F. Valine (33%)

Incorrect
Correct answer
F

33%
Answered correctly

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Time Spent

2023
Version

Explanation

Organic acidemia

Pyrimidines
- Thymidine
- Uracil

Amino acids
- Valine
- Isoleucine
- Methionine
- Threonine

Lipids
- Cholesterol
- Odd-chain fatty acids

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My Notebook
Flashcards
Feedback
Suspend
End Block

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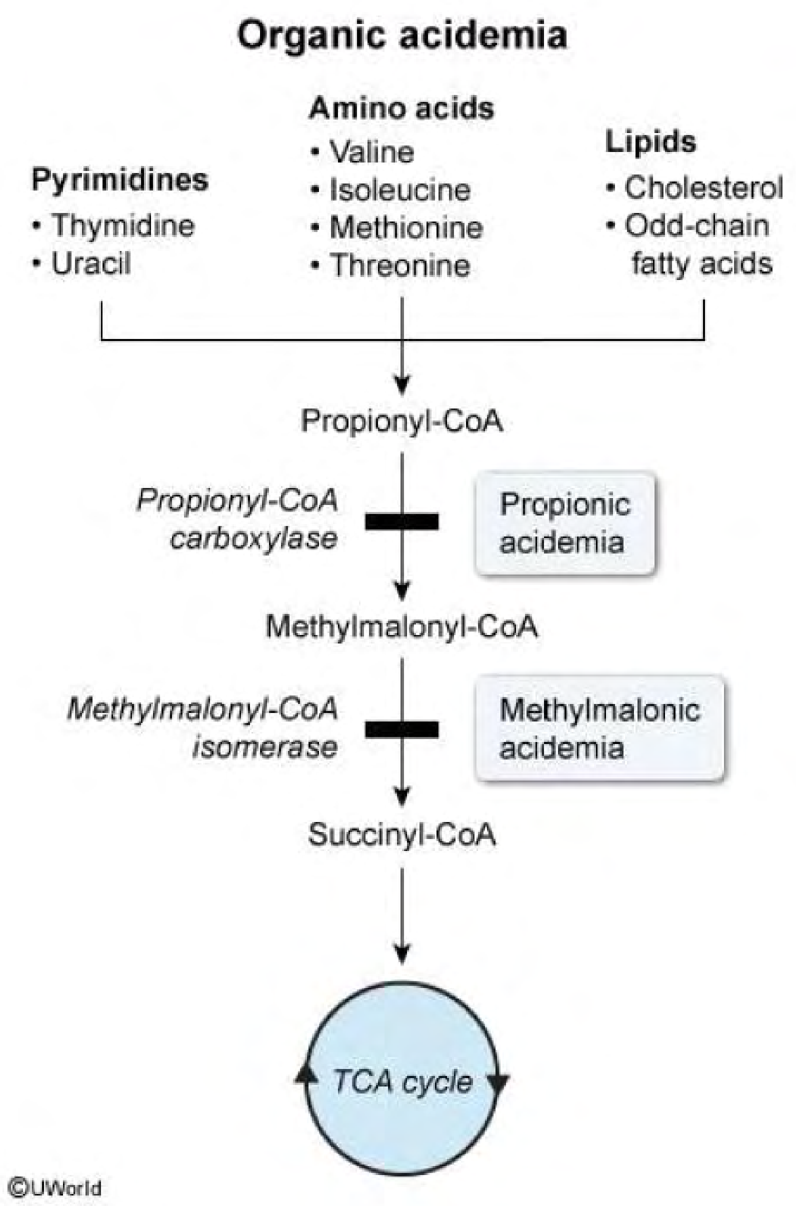
Organic acidemia
Amino acids
• Valine
• Isoleucine
• Methionine
• Threonine
Pyrimidines
• Thymidine
• Uracil
Lipids
• Cholesterol
• Odd-chain fatty acids
Propionyl-CoA
Propionyl-CoA carboxylase
Propionic acidemia
Methylmalonyl-CoA
Methylmalonyl-CoA isomerase
Methylmalonic acidemia
Succinyl-CoA
TCA cycle
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Catab

chain

methy

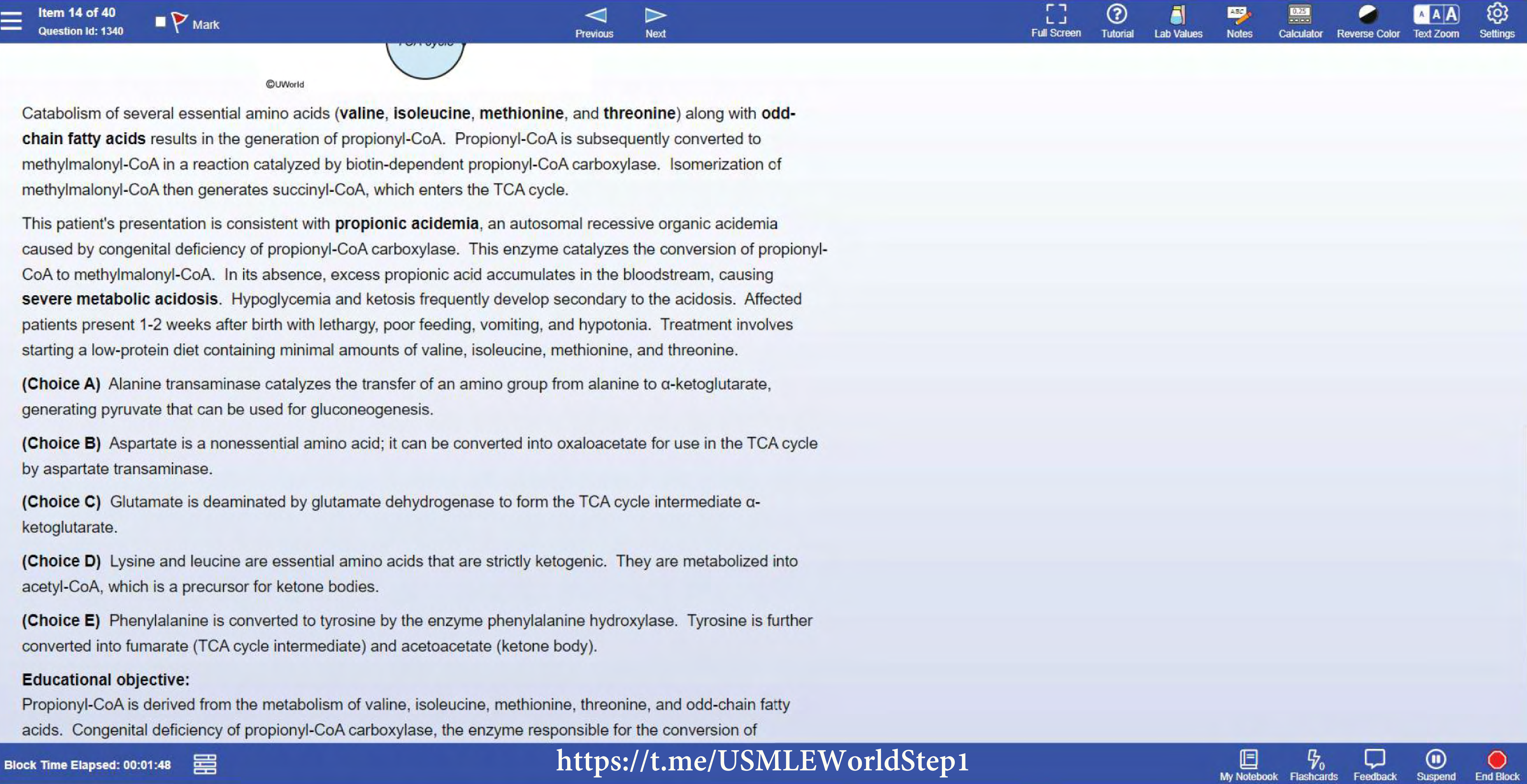
methy

This p

cause

CoA to

severe metabolic acidosis. Hypoglycemia and ketosis frequently develop secondary to the acidosis. Affected



Catabolism of several essential amino acids (**valine**, **isoleucine**, **methionine**, and **threonine**) along with **odd-chain fatty acids** results in the generation of propionyl-CoA. Propionyl-CoA is subsequently converted to methylmalonyl-CoA in a reaction catalyzed by biotin-dependent propionyl-CoA carboxylase. Isomerization of methylmalonyl-CoA then generates succinyl-CoA, which enters the TCA cycle.

This patient's presentation is consistent with **propionic acidemia**, an autosomal recessive organic acidemia caused by congenital deficiency of propionyl-CoA carboxylase. This enzyme catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. In its absence, excess propionic acid accumulates in the bloodstream, causing **severe metabolic acidosis**. Hypoglycemia and ketosis frequently develop secondary to the acidosis. Affected patients present 1-2 weeks after birth with lethargy, poor feeding, vomiting, and hypotonia. Treatment involves starting a low-protein diet containing minimal amounts of valine, isoleucine, methionine, and threonine.

(Choice A) Alanine transaminase catalyzes the transfer of an amino group from alanine to α-ketoglutarate, generating pyruvate that can be used for gluconeogenesis.

(Choice B) Aspartate is a nonessential amino acid; it can be converted into oxaloacetate for use in the TCA cycle by aspartate transaminase.

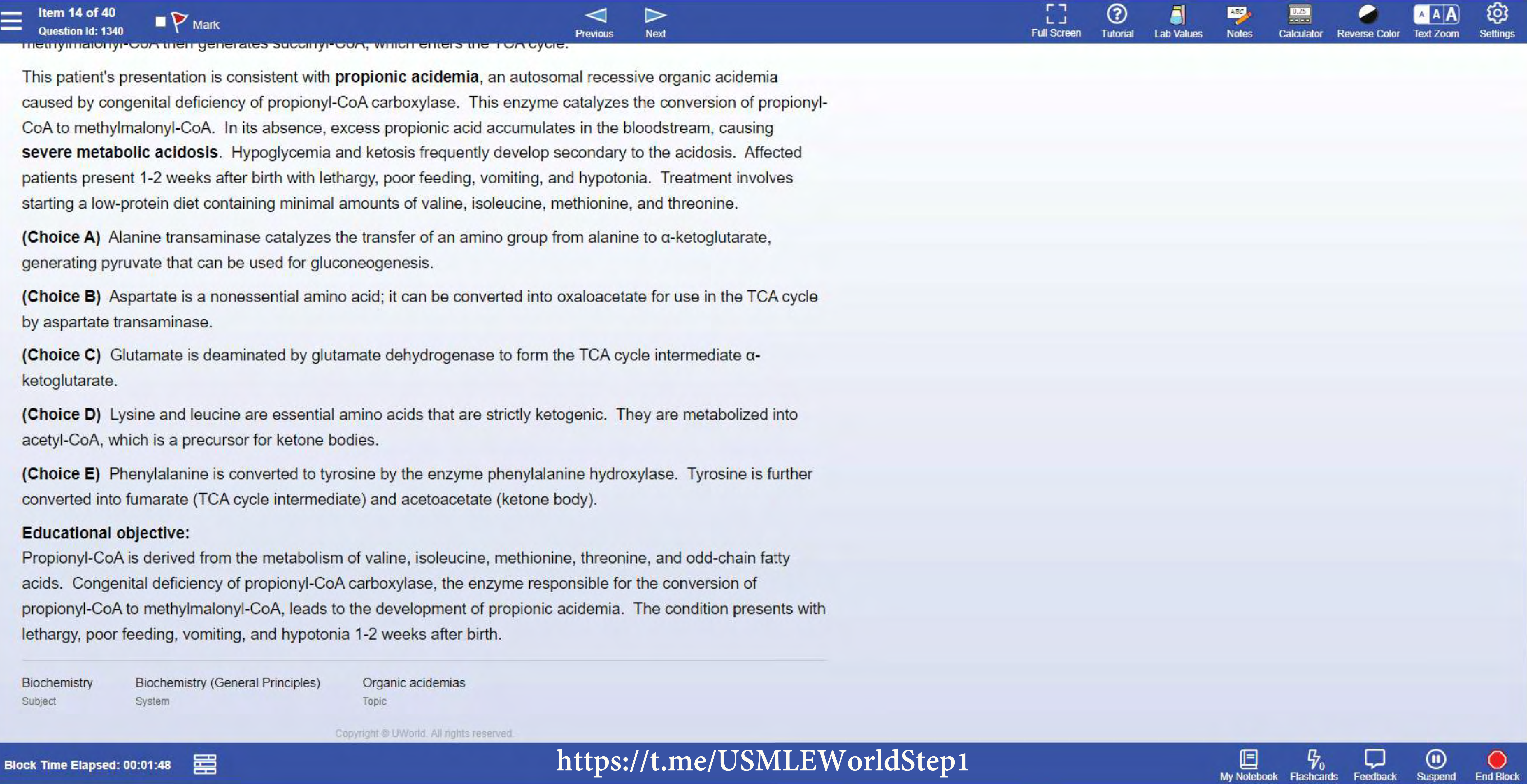
(Choice C) Glutamate is deaminated by glutamate dehydrogenase to form the TCA cycle intermediate α-ketoglutarate.

(Choice D) Lysine and leucine are essential amino acids that are strictly ketogenic. They are metabolized into acetyl-CoA, which is a precursor for ketone bodies.

(Choice E) Phenylalanine is converted to tyrosine by the enzyme phenylalanine hydroxylase. Tyrosine is further converted into fumarate (TCA cycle intermediate) and acetoacetate (ketone body).

Educational objective:

Propionyl-CoA is derived from the metabolism of valine, isoleucine, methionine, threonine, and odd-chain fatty acids. Congenital deficiency of propionyl-CoA carboxylase, the enzyme responsible for the conversion of



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(Choice E) Phenylalanine is converted to tyrosine by the enzyme phenylalanine hydroxylase. Tyrosine is further converted into fumarate (TCA cycle intermediate) and acetoacetate (ketone body).

Educational objective:
Propionyl-CoA is derived from the metabolism of valine, isoleucine, methionine, threonine, and odd-chain fatty acids. Congenital deficiency of propionyl-CoA carboxylase, the enzyme responsible for the conversion of propionyl-CoA to methylmalonyl-CoA, leads to the development of propionic acidemia. The condition presents with lethargy, poor feeding, vomiting, and hypotonia 1-2 weeks after birth.

Biochemistry	Biochemistry (General Principles)	Organic acidemias
Subject	System	Topic

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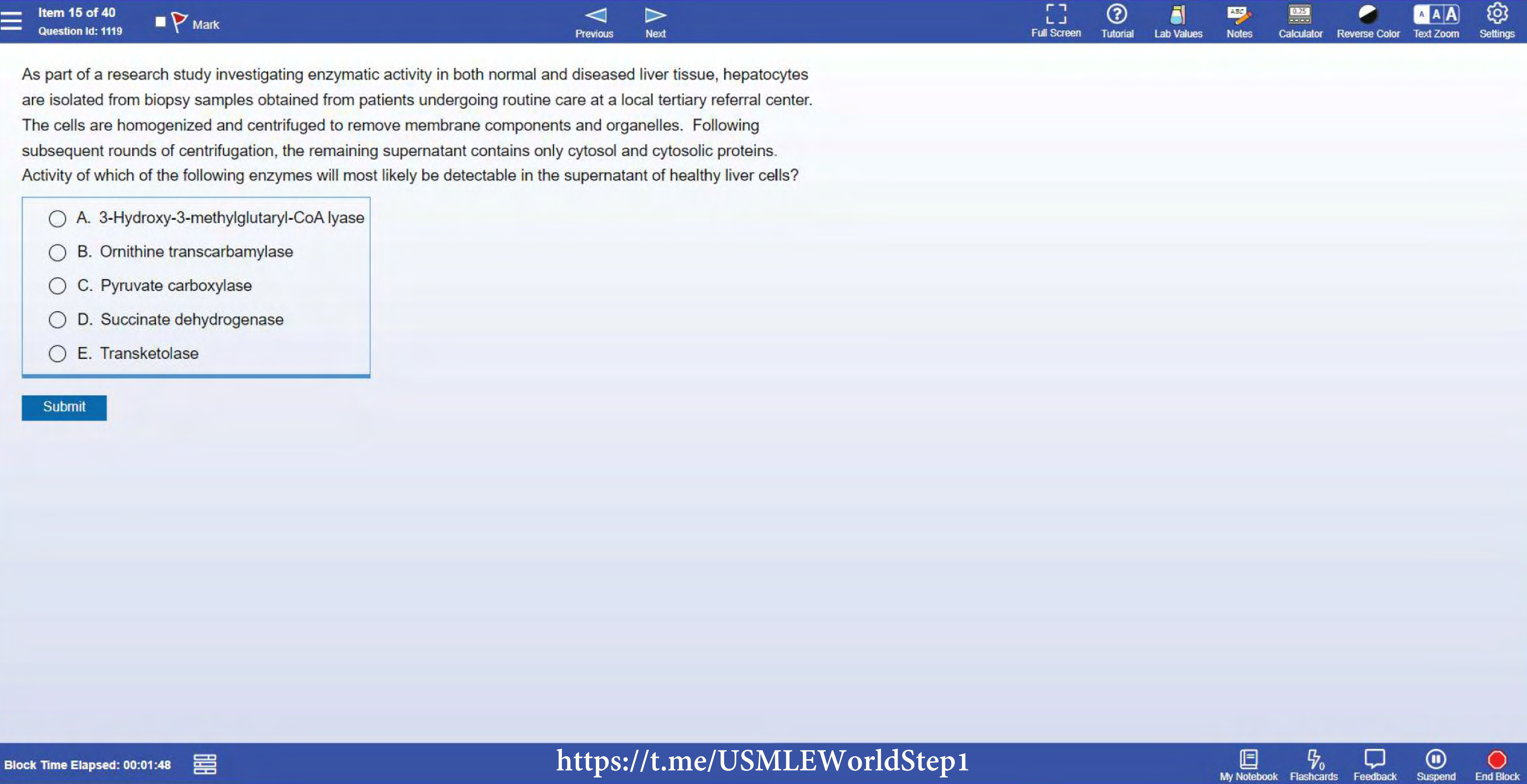
Item 15 of 40
Question Id: 1119
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

- ○ A. 3-Hydroxy-3-methylglutaryl-CoA lyase
- ○ B. Ornithine transcarbamylase
- ○ C. Pyruvate carboxylase
- ○ D. Succinate dehydrogenase
- ○ E. Transketolase

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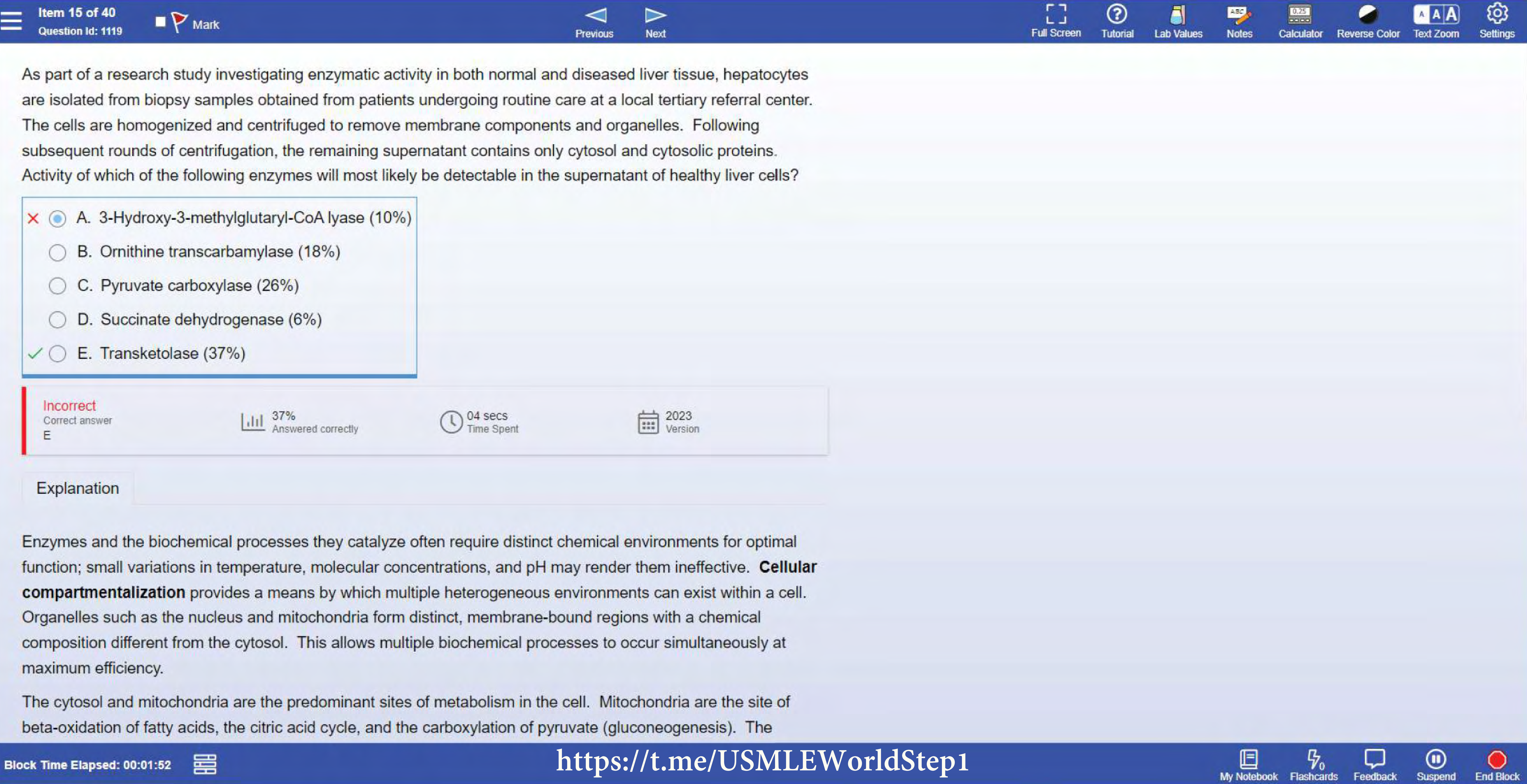
Flashcards
Feedback
Suspend
End Block


Item 15 of 40
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Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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✗ ● A. 3-Hydroxy-3-methylglutaryl-CoA lyase (10%)
○ B. Ornithine transcarbamylase (18%)
○ C. Pyruvate carboxylase (26%)
○ D. Succinate dehydrogenase (6%)
✓ ○ E. Transketolase (37%)

Incorrect
Correct answer
E

37%
Answered correctly

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2023
Version

Explanation

Enzymes and the biochemical processes they catalyze often require distinct chemical environments for optimal function; small variations in temperature, molecular concentrations, and pH may render them ineffective. **Cellular compartmentalization** provides a means by which multiple heterogeneous environments can exist within a cell. Organelles such as the nucleus and mitochondria form distinct, membrane-bound regions with a chemical composition different from the cytosol. This allows multiple biochemical processes to occur simultaneously at maximum efficiency.

The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the citric acid cycle, and the carboxylation of pyruvate (gluconeogenesis). The

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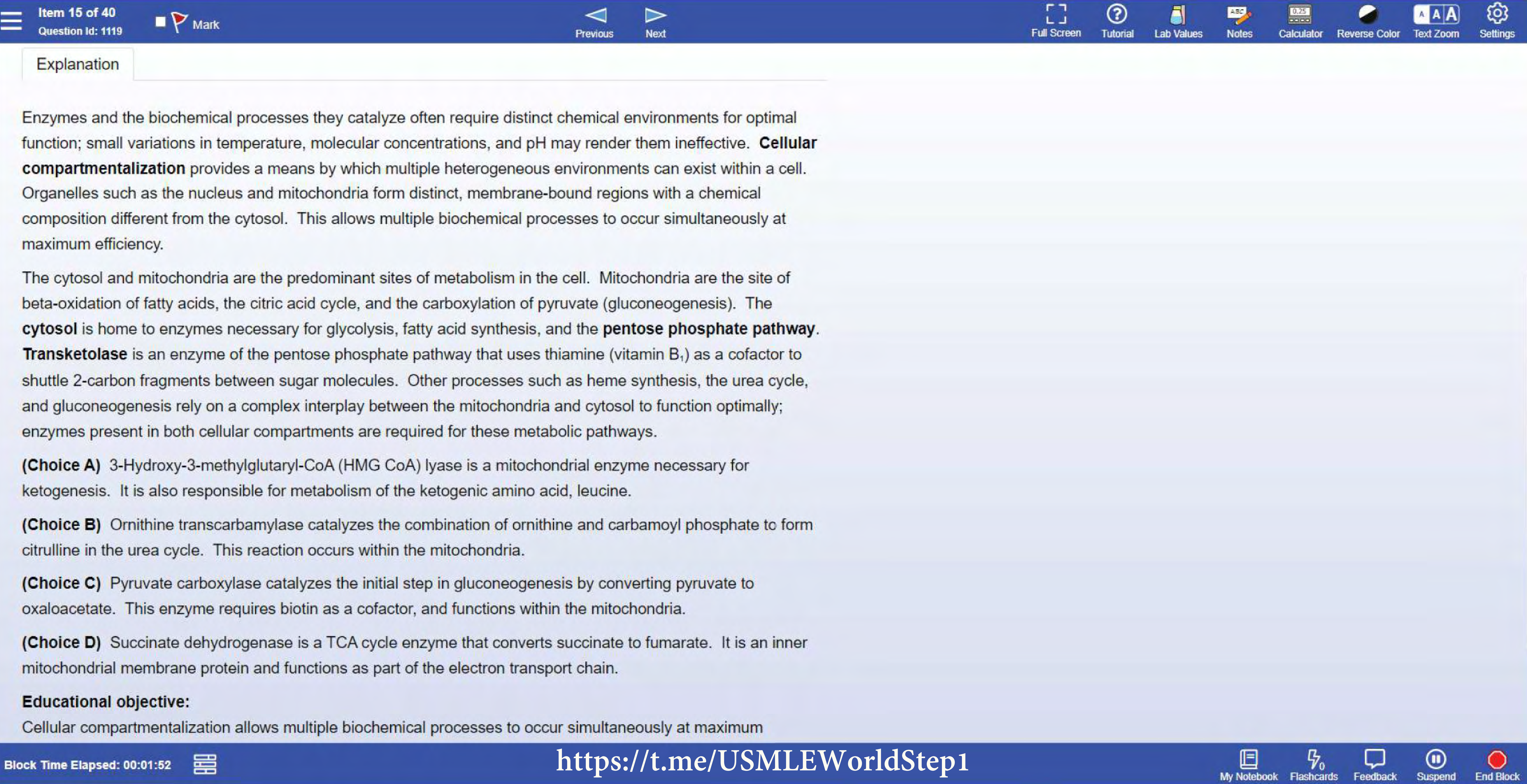
My Notebook
Flashcards
Feedback
Suspend
End Block



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The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the citric acid cycle, and the carboxylation of pyruvate (gluconeogenesis). The **cytosol** is home to enzymes necessary for glycolysis, fatty acid synthesis, and the **pentose phosphate pathway**. **Transketolase** is an enzyme of the pentose phosphate pathway that uses thiamine (vitamin B_1) as a cofactor to shuttle 2-carbon fragments between sugar molecules. Other processes such as heme synthesis, the urea cycle, and gluconeogenesis rely on a complex interplay between the mitochondria and cytosol to function optimally; enzymes present in both cellular compartments are required for these metabolic pathways.

(Choice A) 3-Hydroxy-3-methylglutaryl-CoA (HMG CoA) lyase is a mitochondrial enzyme necessary for ketogenesis. It is also responsible for metabolism of the ketogenic amino acid, leucine.

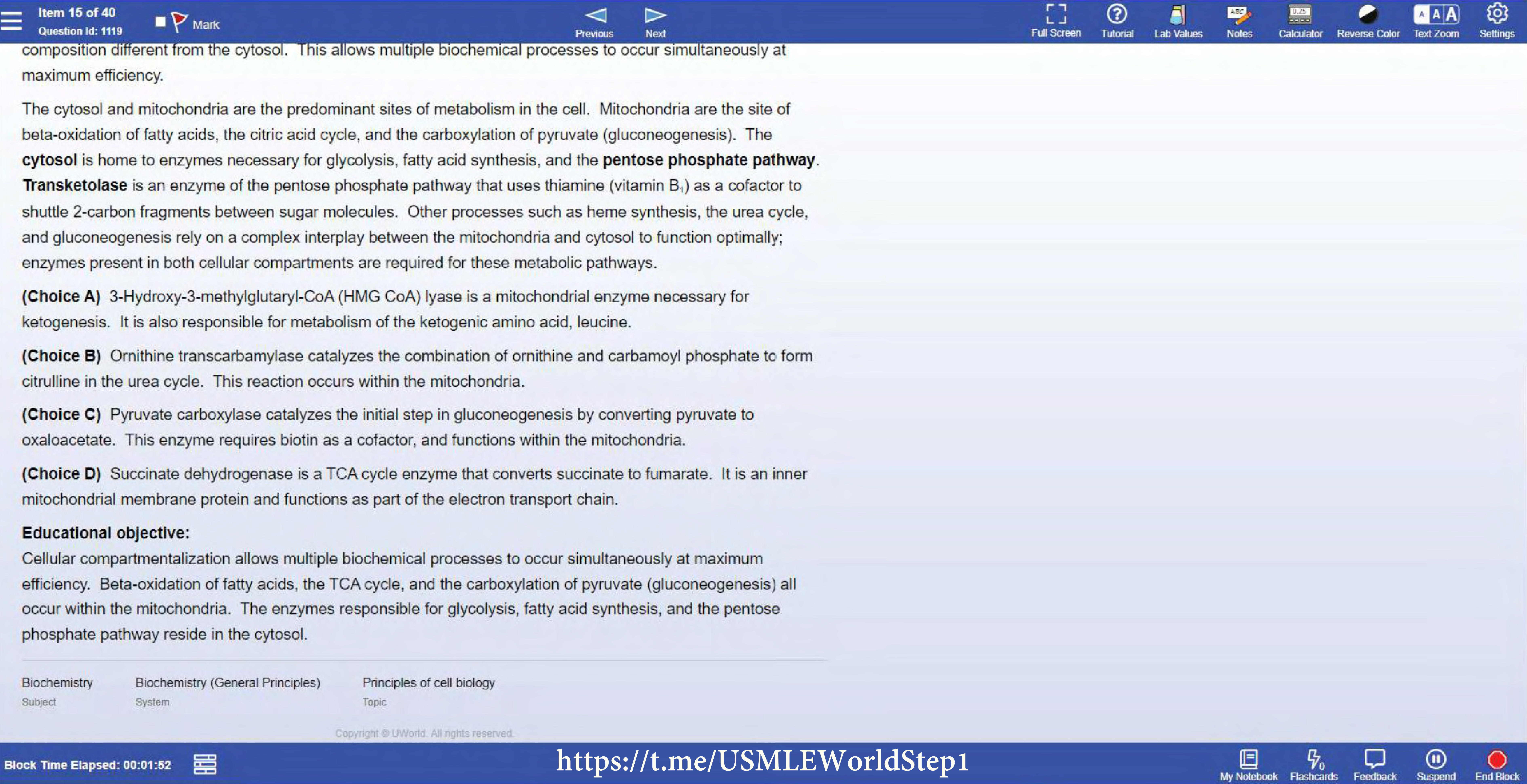
(Choice B) Ornithine transcarbamylase catalyzes the combination of ornithine and carbamoyl phosphate to form citrulline in the urea cycle. This reaction occurs within the mitochondria.

(Choice C) Pyruvate carboxylase catalyzes the initial step in gluconeogenesis by converting pyruvate to oxaloacetate. This enzyme requires biotin as a cofactor, and functions within the mitochondria.

(Choice D) Succinate dehydrogenase is a TCA cycle enzyme that converts succinate to fumarate. It is an inner mitochondrial membrane protein and functions as part of the electron transport chain.

Educational objective:

Cellular compartmentalization allows multiple biochemical processes to occur simultaneously at maximum



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(Choice D) Succinate dehydrogenase is a TCA cycle enzyme that converts succinate to fumarate. It is an inner mitochondrial membrane protein and functions as part of the electron transport chain.

Educational objective:
Cellular compartmentalization allows multiple biochemical processes to occur simultaneously at maximum efficiency. Beta-oxidation of fatty acids, the TCA cycle, and the carboxylation of pyruvate (gluconeogenesis) all occur within the mitochondria. The enzymes responsible for glycolysis, fatty acid synthesis, and the pentose phosphate pathway reside in the cytosol.

Biochemistry	Biochemistry (General Principles)	Principles of cell biology
Subject	System	Topic

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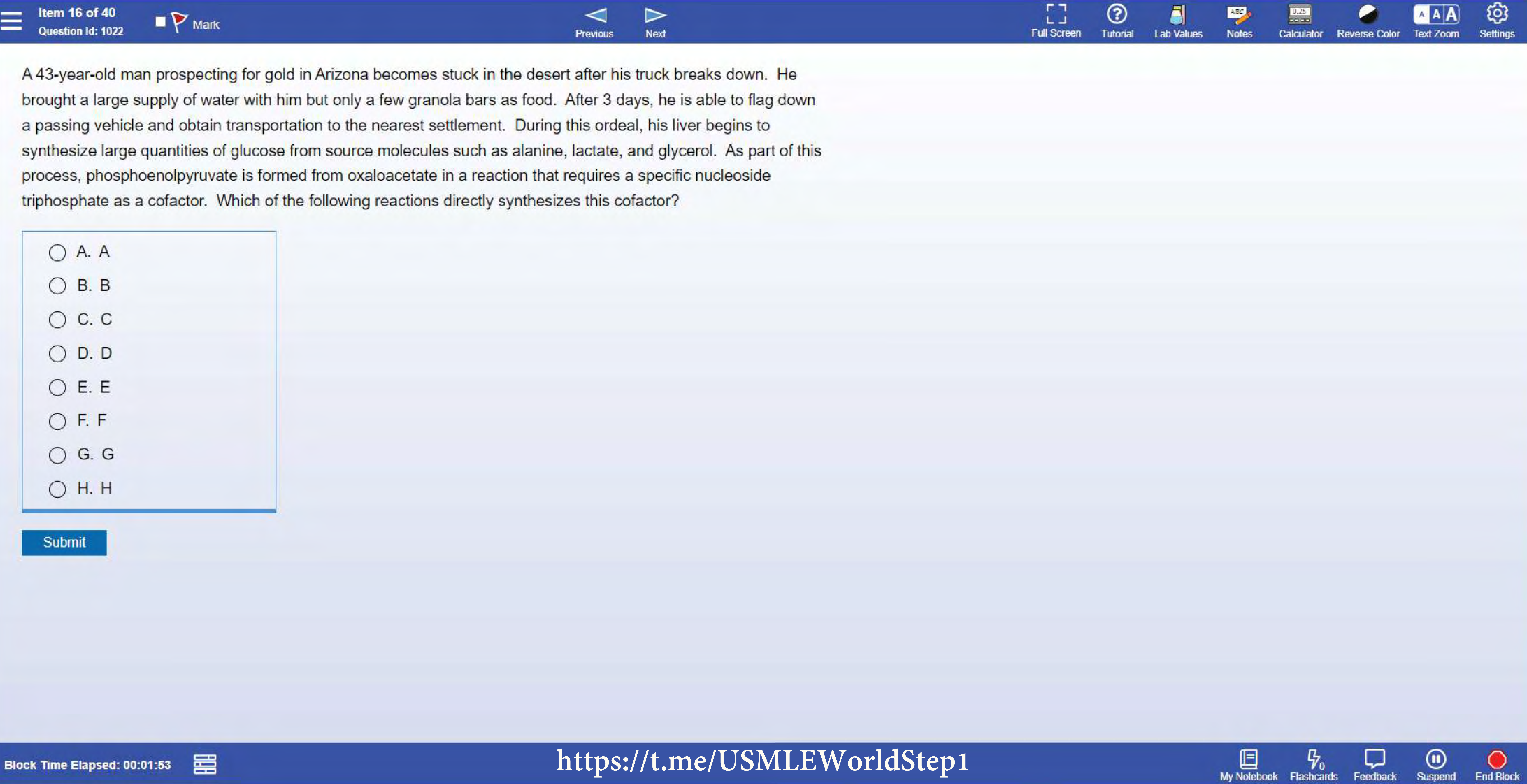
Item 16 of 40
Question Id: 1022
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 43-year-old man prospecting for gold in Arizona becomes stuck in the desert after his truck breaks down. He brought a large supply of water with him but only a few granola bars as food. After 3 days, he is able to flag down a passing vehicle and obtain transportation to the nearest settlement. During this ordeal, his liver begins to synthesize large quantities of glucose from source molecules such as alanine, lactate, and glycerol. As part of this process, phosphoenolpyruvate is formed from oxaloacetate in a reaction that requires a specific nucleoside triphosphate as a cofactor. Which of the following reactions directly synthesizes this cofactor?

○ A. A
○ B. B
○ C. C
○ D. D
○ E. E
○ F. F
○ G. G
○ H. H

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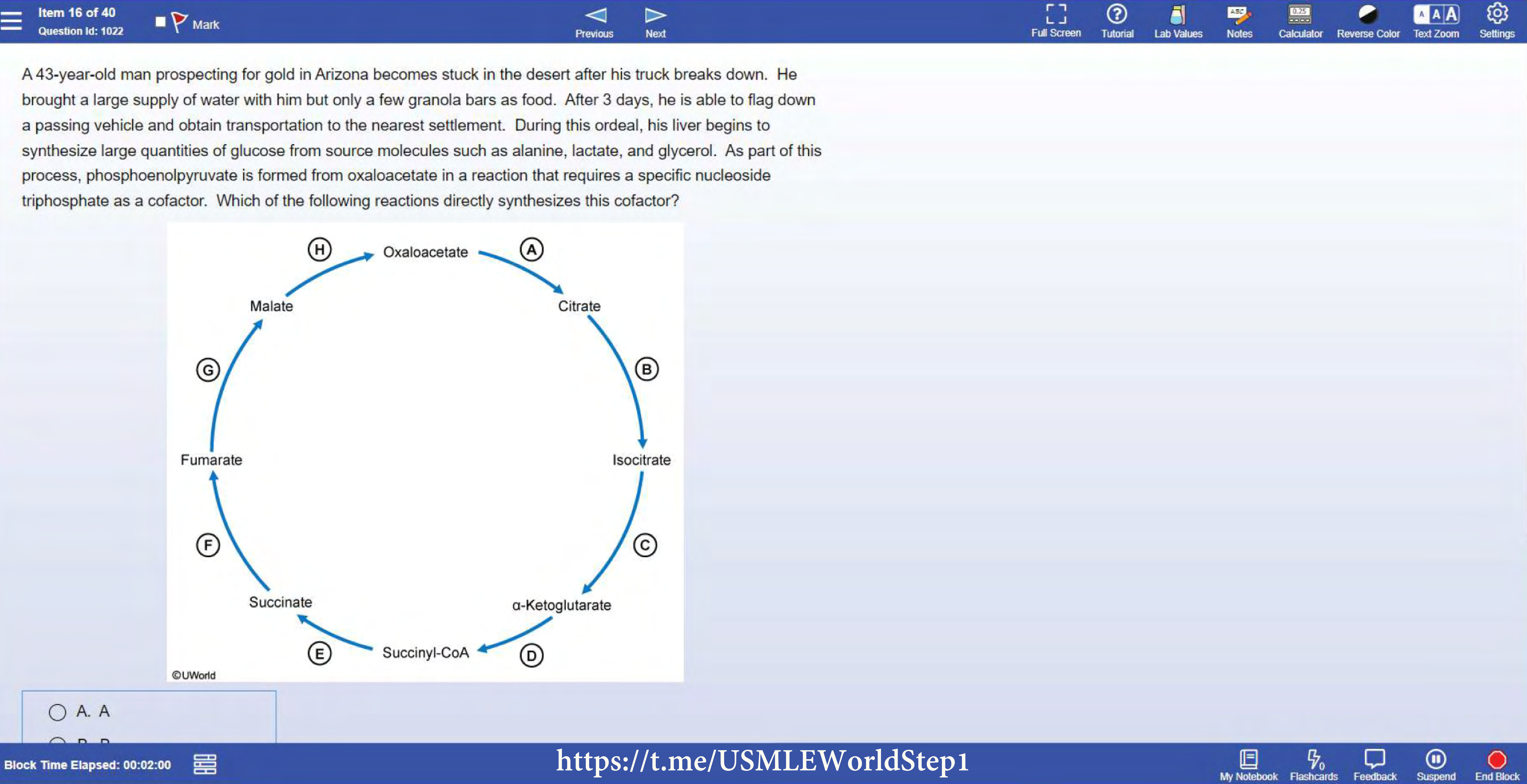
My Notebook
Flashcards
Feedback
Suspend
End Block


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Item 16 of 40
Question Id: 1022

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Oxaloacetate
Ⓐ
Citrate
Ⓑ
Isocitrate
Ⓒ
α-Ketoglutarate
Ⓓ
Succinyl-CoA
Ⓔ
Succinate
Ⓕ
Fumarate
Ⓖ
Malate
Ⓗ

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○ A. A

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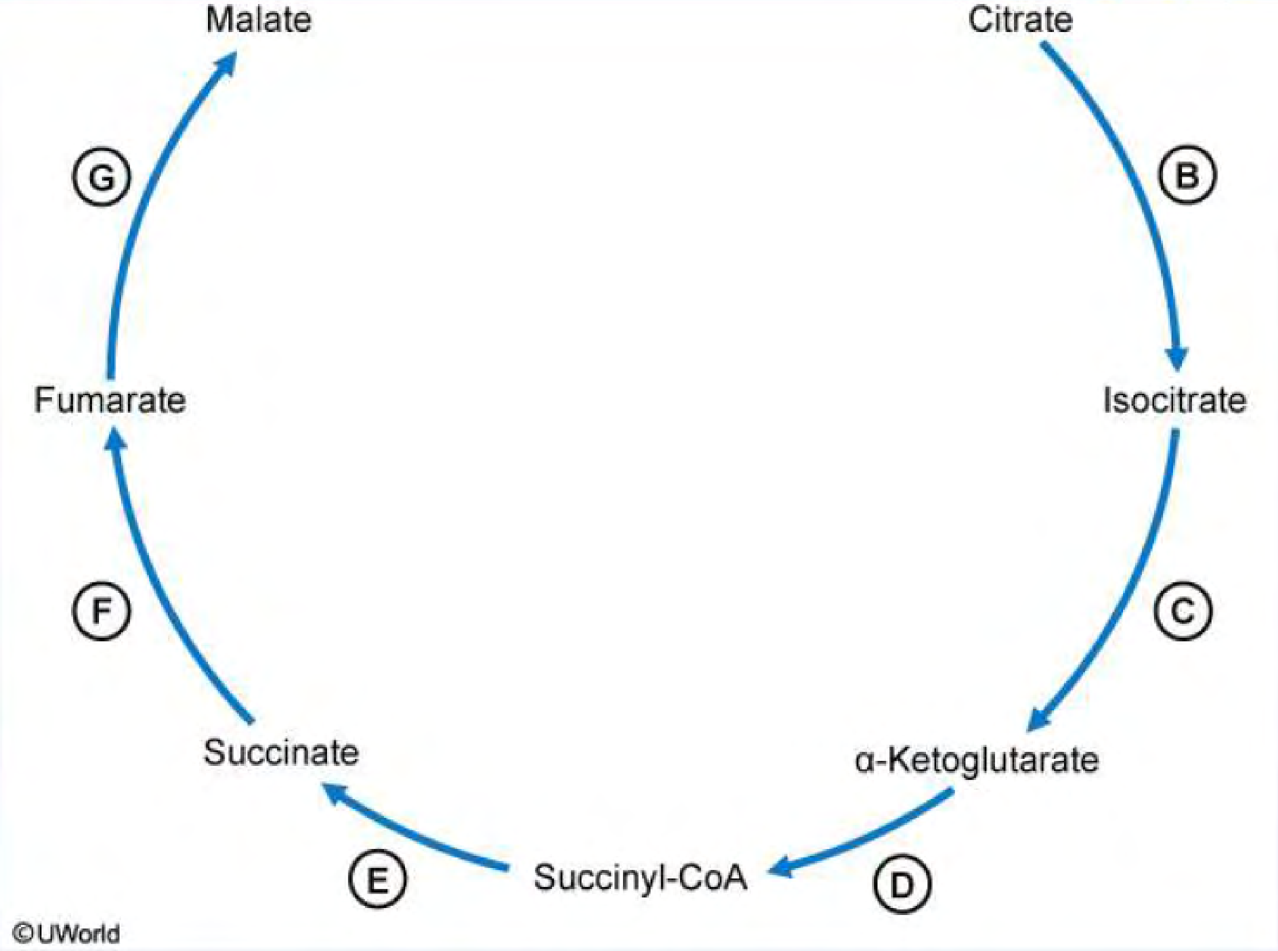
Flashcards
Feedback
Suspend
End Block


Malate
Citrate
G
B
Fumarate
Isocitrate
F
C
Succinate
α-Ketoglutarate
E
Succinyl-CoA
D

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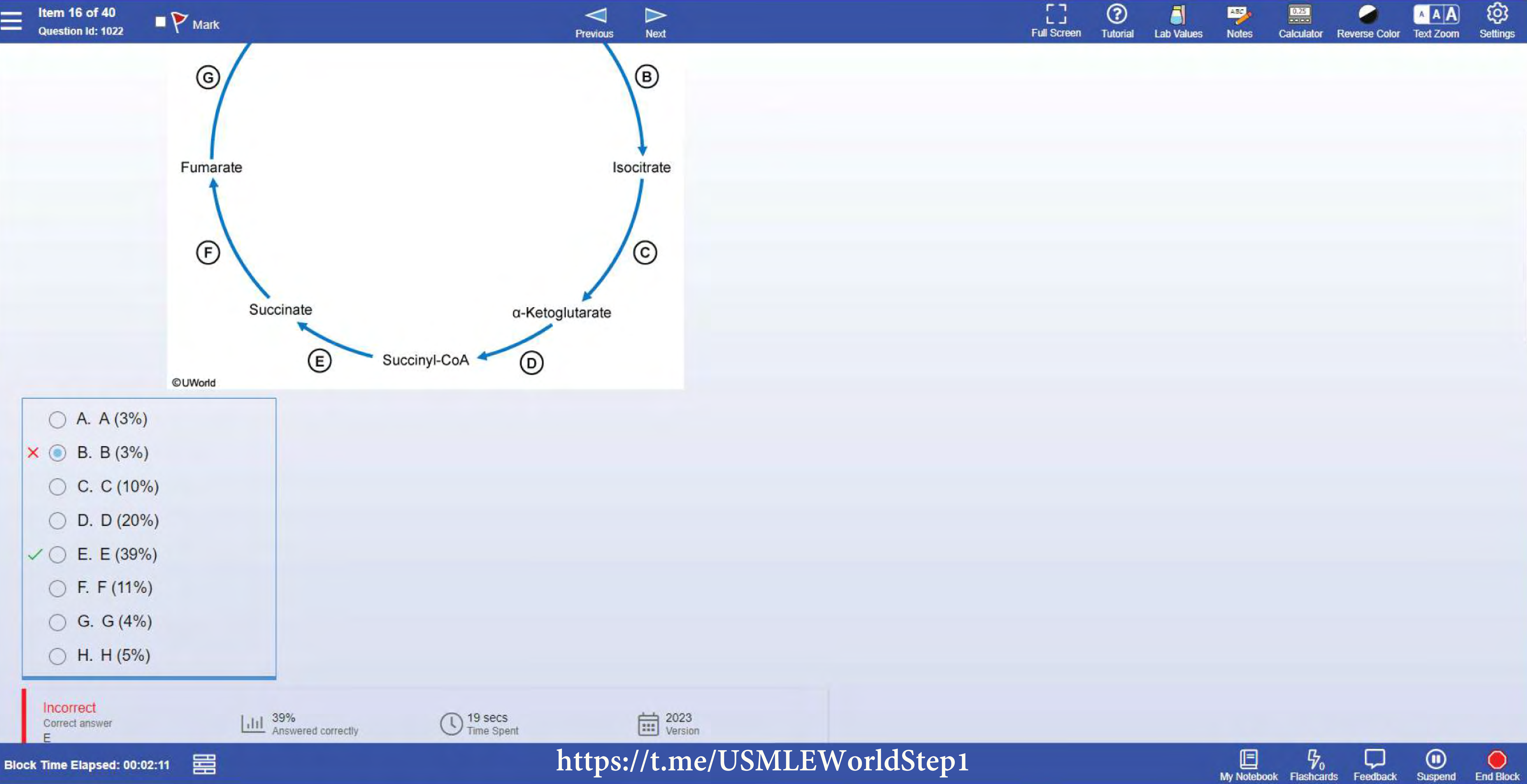
○ A. A
○ B. B
○ C. C
○ D. D
○ E. E
○ F. F
○ G. G
○ H. H


Item 16 of 40
Question Id: 1022
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
G
B
Fumarate
Isocitrate
F
C
Succinate
α-Ketoglutarate
E
Succinyl-CoA
D
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My Notebook
Flashcards
Feedback
Suspend
End Block

○ A. A (3%)

✗ ● B. B (3%)

○ C. C (10%)

○ D. D (20%)

✓ ○ E. E (39%)

○ F. F (11%)

○ G. G (4%)

○ H. H (5%)

Incorrect
Correct answer
E

39%
Answered correctly

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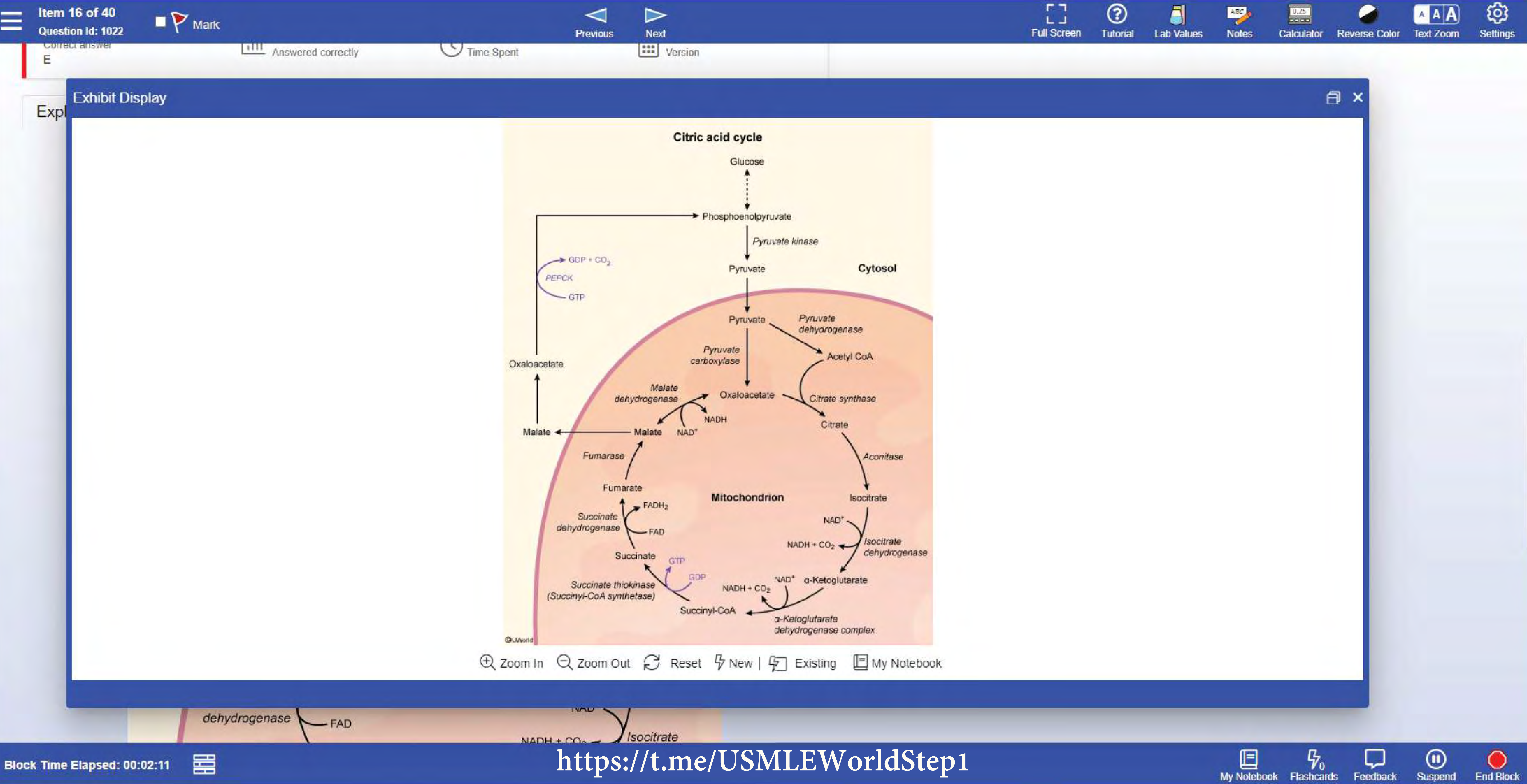
2023
Version

Block Time Elapsed: 00:02:11



Item 16 of 40

Question Id: 1022

Correct answer

E

Block Time Elapsed: 00:02:11

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Answered correctly
Time Spent
Version
Expl
Exhibit Display
Citric acid cycle
Glucose
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
Cytosol
GDP + CO2
PEPCK
GTP
Pyruvate
Pyruvate dehydrogenase
Acetyl CoA
Pyruvate carboxylase
Oxaloacetate
Malate dehydrogenase
Oxaloacetate
Citrate synthase
NADH
Malate
Malate
NAD+
Citrate
Fumarase
Aconitase
Fumarate
Mitochondrion
Isocitrate
FADH2
Succinate dehydrogenase
FAD
NAD+
NADH + CO2
Isocitrate dehydrogenase
Succinate
GTP
GDP
NAD+
α-Ketoglutarate
NADH + CO2
Succinate thiokinase (Succinyl-CoA synthetase)
Succinyl-CoA
α-Ketoglutarate dehydrogenase complex
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Zoom In
Zoom Out
Reset
New
Existing
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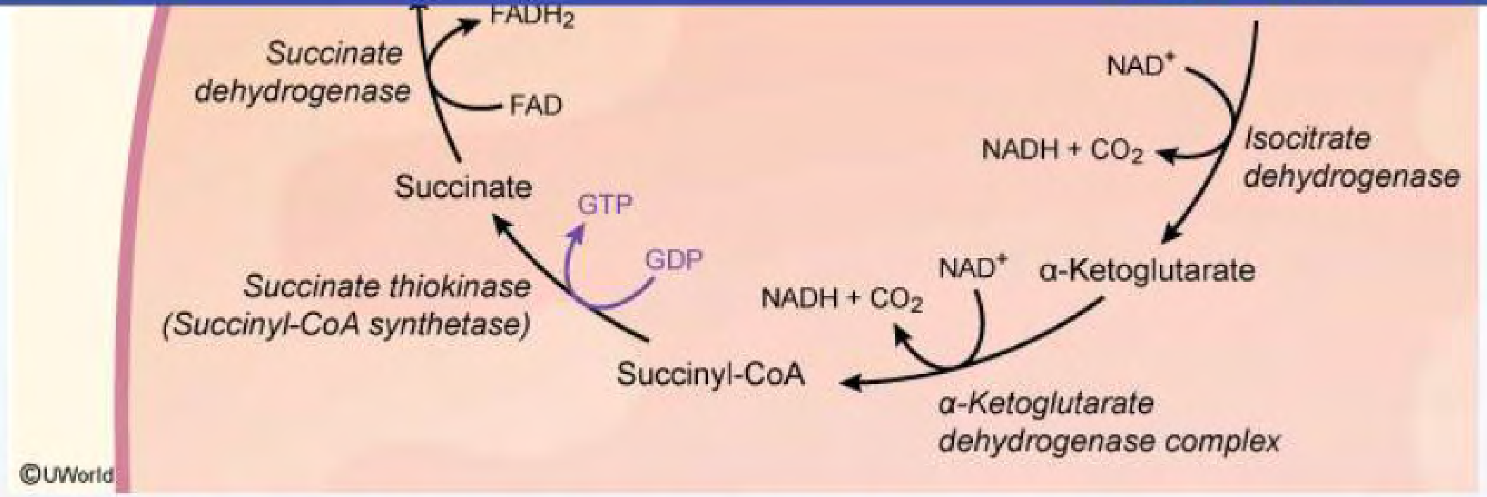
FAD
NAD
NADH + CO2
Isocitrate
My Notebook
Flashcards
Feedback
Suspend
End Block


FADH₂
Succinate dehydrogenase
FAD
Succinate
GTP
GDP
Succinate thiokinase (Succinyl-CoA synthetase)
Succinyl-CoA
NAD⁺
NADH + CO₂
Isocitrate dehydrogenase
NAD⁺
NADH + CO₂
α-Ketoglutarate
α-Ketoglutarate dehydrogenase complex
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The majority of ATP used for cellular processes is generated by the oxidation of acetate in the tricarboxylic acid (TCA) cycle. The enzymes of the TCA cycle are located in the mitochondria and generate reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) **(Choices C, D, F, and H)**. These molecules drive the process of oxidative phosphorylation, which converts their reducing potential into high-energy ATP via the electron transport chain.

ATP can also be generated by **substrate-level phosphorylation**, which involves the direct transfer of a phosphate group from a reactive intermediate to a nucleotide diphosphate (eg, ADP, GDP). **Succinyl-CoA synthetase** converts succinyl-CoA to succinate and uses the high-energy thioester present in succinyl-CoA to drive **GTP synthesis**. This GTP can then be used to transphosphorylate ADP to ATP, or it may be utilized by specific GTP-hydrolyzing enzymes, such as **phosphoenolpyruvate carboxykinase** (converts oxaloacetate to phosphoenolpyruvate during gluconeogenesis).

Educational objective:

GTP is synthesized by succinyl-CoA synthetase during the conversion of succinyl-CoA to succinate in the citric acid cycle. During gluconeogenesis, phosphoenolpyruvate carboxykinase uses GTP to synthesize phosphoenolpyruvate from oxaloacetate.

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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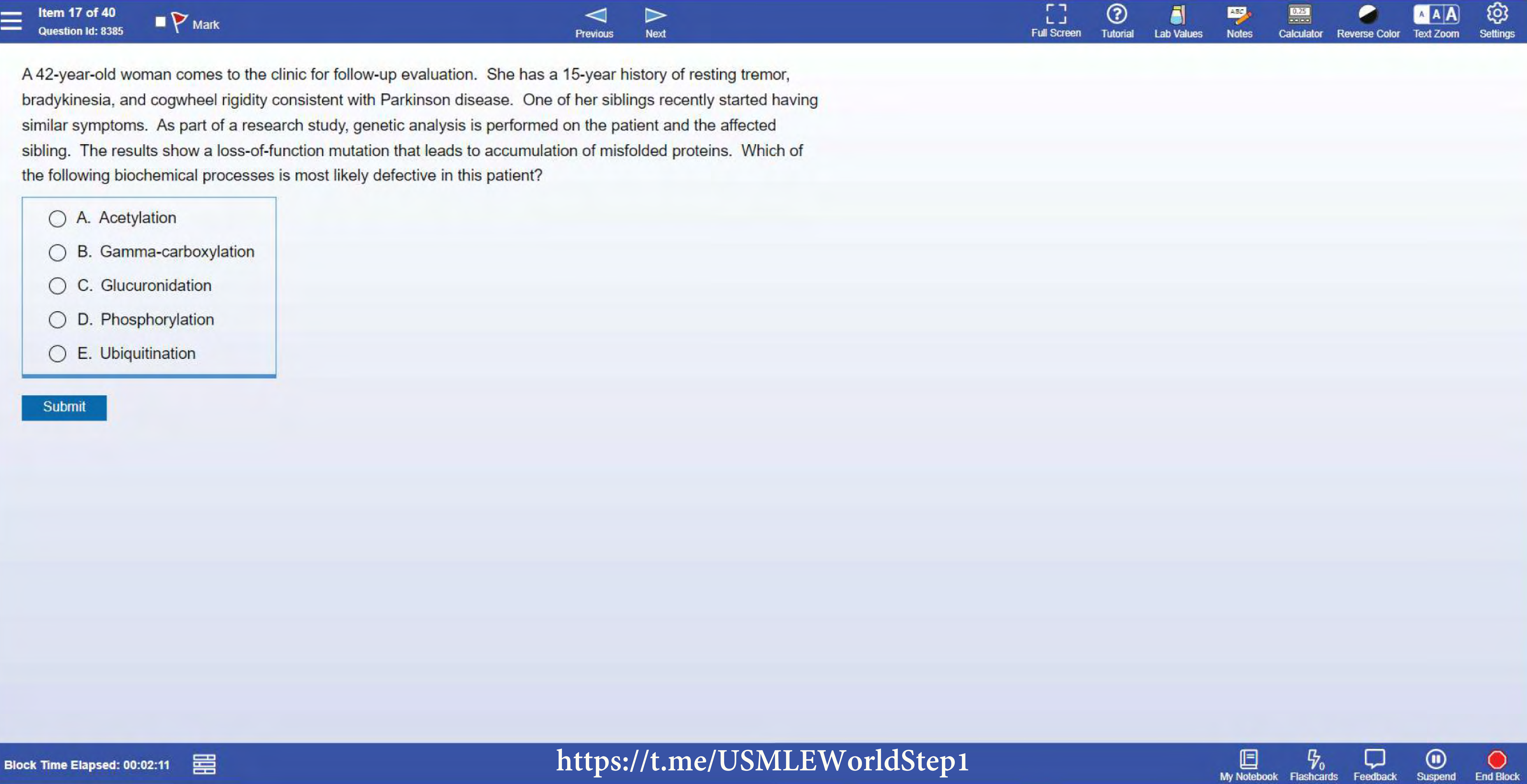
Item 17 of 40
Question Id: 8385
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 42-year-old woman comes to the clinic for follow-up evaluation. She has a 15-year history of resting tremor, bradykinesia, and cogwheel rigidity consistent with Parkinson disease. One of her siblings recently started having similar symptoms. As part of a research study, genetic analysis is performed on the patient and the affected sibling. The results show a loss-of-function mutation that leads to accumulation of misfolded proteins. Which of the following biochemical processes is most likely defective in this patient?

○ A. Acetylation
○ B. Gamma-carboxylation
○ C. Glucuronidation
○ D. Phosphorylation
○ E. Ubiquitination

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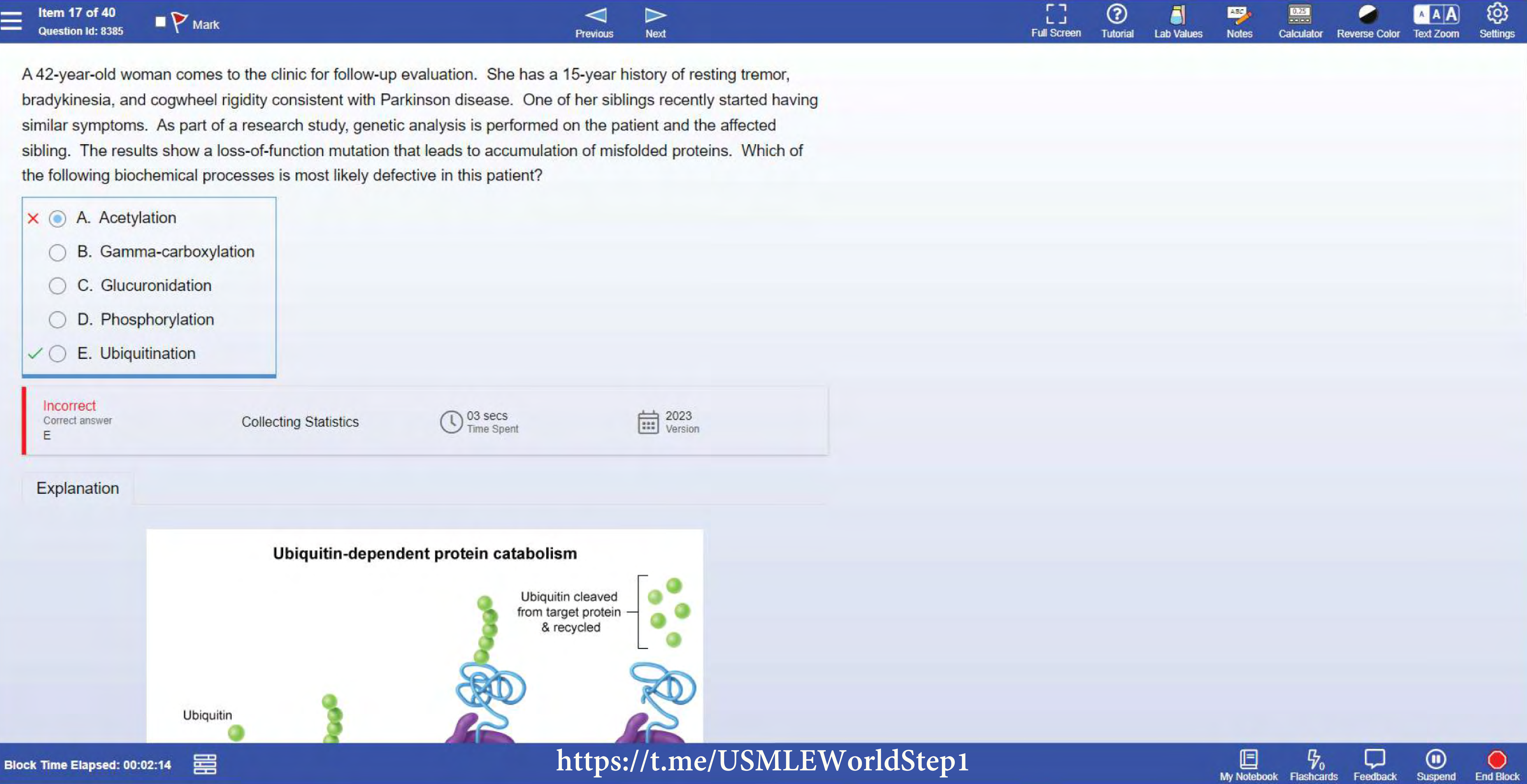
Block Time Elapsed: 00:02:11
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 17 of 40
Question Id: 8385
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
Settings

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- ○ B. Gamma-carboxylation
- ○ C. Glucuronidation
- ○ D. Phosphorylation
- ✓ ○ E. Ubiquitination

Incorrect
Correct answer
E

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Time Spent

2023
Version

Explanation

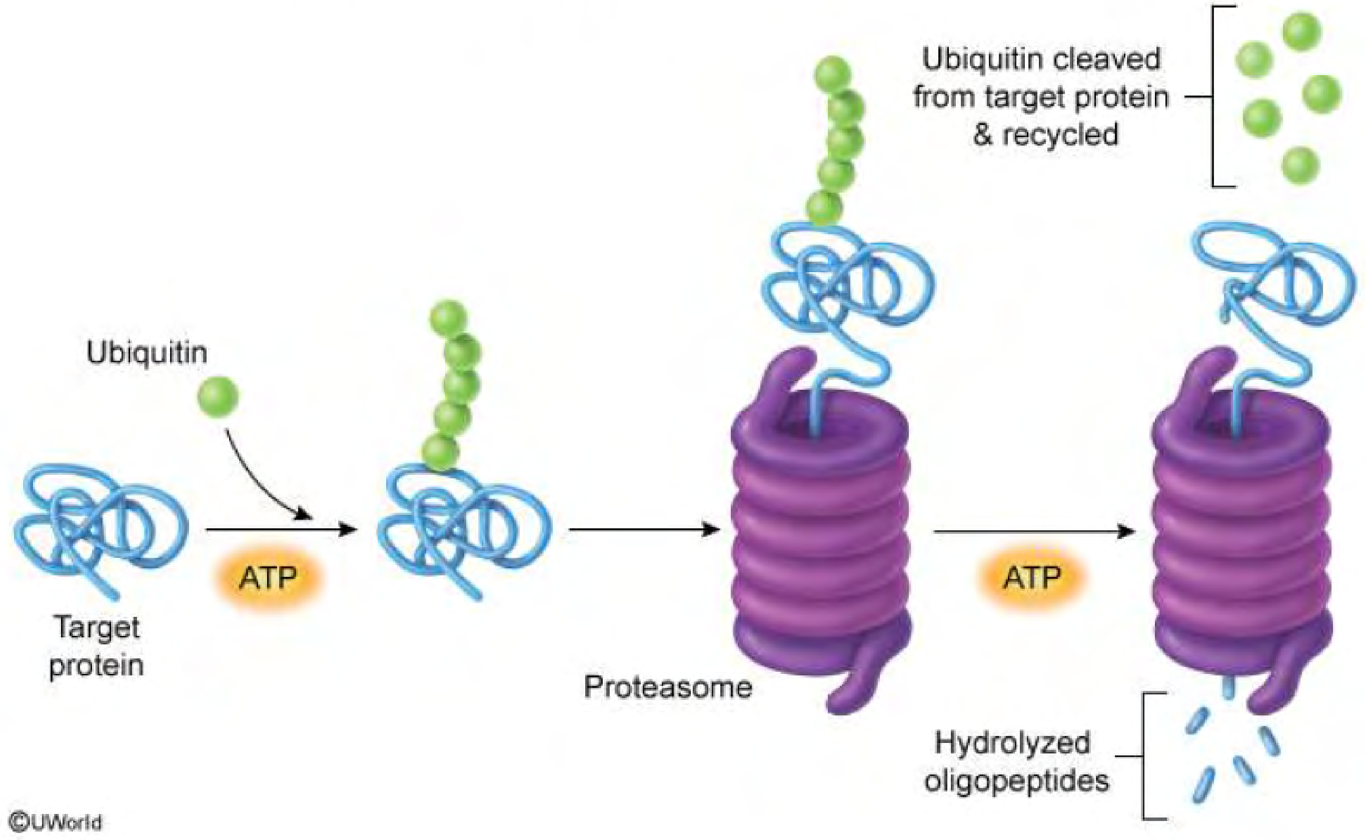
Ubiquitin-dependent protein catabolism

Ubiquitin cleaved from target protein & recycled
Ubiquitin

Block Time Elapsed: 00:02:14
My Notebook
Flashcards
Feedback
Suspend
End Block

Exhibit Display

Ubiquitin-dependent protein catabolism


Ubiquitin cleaved
from target protein
& recycled
Ubiquitin
Target
protein
ATP
Proteasome
ATP
Hydrolyzed
oligopeptides

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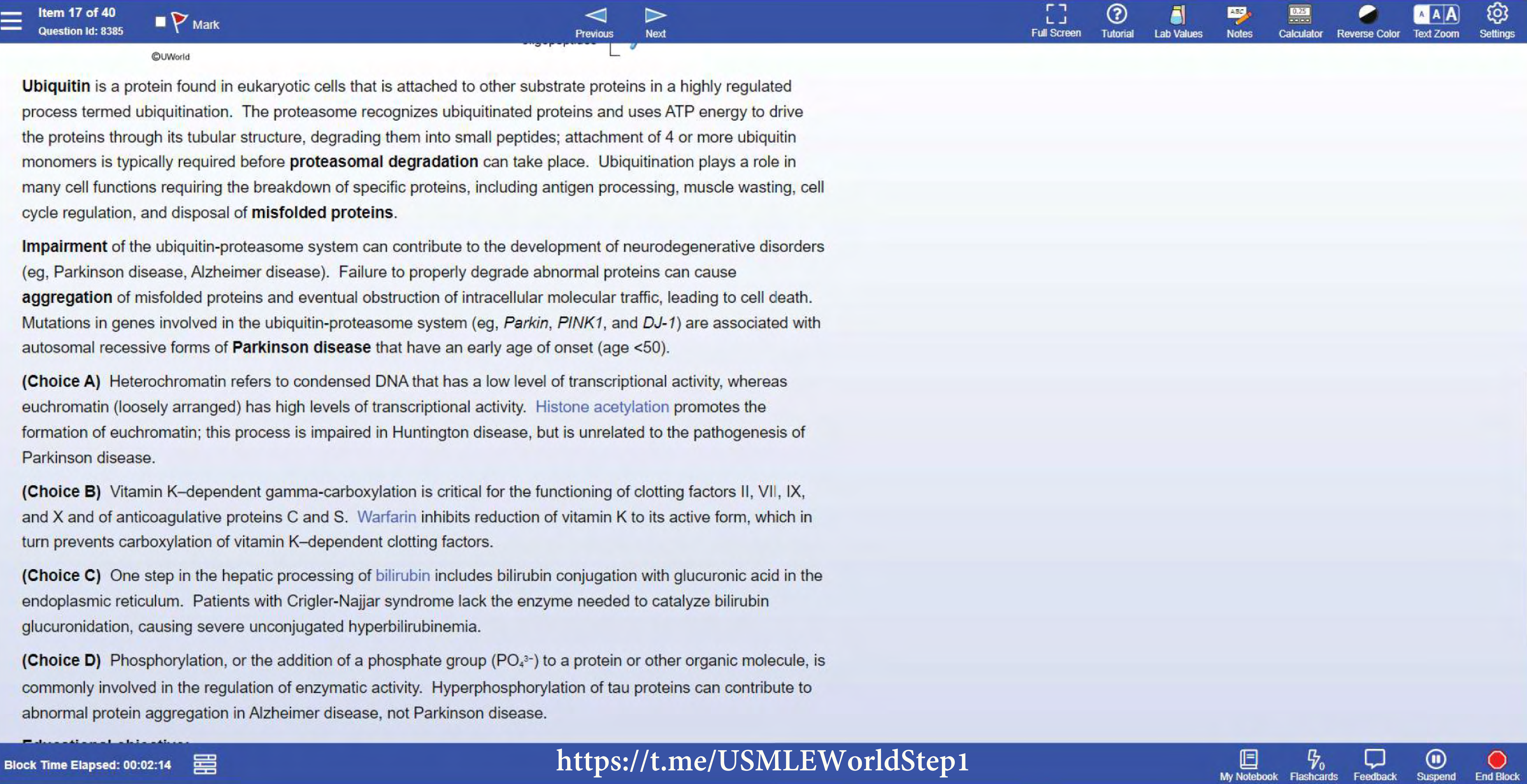
Parkinson disease.



Ubiquitin is a protein found in eukaryotic cells that is attached to other substrate proteins in a highly regulated process termed ubiquitination. The proteasome recognizes ubiquitinated proteins and uses ATP energy to drive the proteins through its tubular structure, degrading them into small peptides; attachment of 4 or more ubiquitin monomers is typically required before **proteasomal degradation** can take place. Ubiquitination plays a role in many cell functions requiring the breakdown of specific proteins, including antigen processing, muscle wasting, cell cycle regulation, and disposal of **misfolded proteins**.

Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders (eg, Parkinson disease, Alzheimer disease). Failure to properly degrade abnormal proteins can cause **aggregation** of misfolded proteins and eventual obstruction of intracellular molecular traffic, leading to cell death. Mutations in genes involved in the ubiquitin-proteasome system (eg, *Parkin*, *PINK1*, and *DJ-1*) are associated with autosomal recessive forms of **Parkinson disease** that have an early age of onset (age <50).

(Choice A) Heterochromatin refers to condensed DNA that has a low level of transcriptional activity, whereas euchromatin (loosely arranged) has high levels of transcriptional activity. Histone acetylation promotes the formation of euchromatin; this process is impaired in Huntington disease, but is unrelated to the pathogenesis of Parkinson disease.

(Choice B) Vitamin K–dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X and of anticoagulative proteins C and S. Warfarin inhibits reduction of vitamin K to its active form, which in turn prevents carboxylation of vitamin K–dependent clotting factors.

(Choice C) One step in the hepatic processing of bilirubin includes bilirubin conjugation with glucuronic acid in the endoplasmic reticulum. Patients with Crigler-Najjar syndrome lack the enzyme needed to catalyze bilirubin glucuronidation, causing severe unconjugated hyperbilirubinemia.

(Choice D) Phosphorylation, or the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule, is commonly involved in the regulation of enzymatic activity. Hyperphosphorylation of tau proteins can contribute to abnormal protein aggregation in Alzheimer disease, not Parkinson disease.

Item 17 of 40
Question Id: 8385
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:02:14
My Notebook
Flashcards
Feedback
Suspend
End Block

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(Choice B) Vitamin K–dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X and of anticoagulative proteins C and S. Warfarin inhibits reduction of vitamin K to its active form, which in turn prevents carboxylation of vitamin K–dependent clotting factors.

(Choice C) One step in the hepatic processing of bilirubin includes bilirubin conjugation with glucuronic acid in the endoplasmic reticulum. Patients with Crigler-Najjar syndrome lack the enzyme needed to catalyze bilirubin glucuronidation, causing severe unconjugated hyperbilirubinemia.

(Choice D) Phosphorylation, or the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule, is commonly involved in the regulation of enzymatic activity. Hyperphosphorylation of tau proteins can contribute to abnormal protein aggregation in Alzheimer disease, not Parkinson disease.

Educational objective:

Ubiquitin is a protein that undergoes attachment to other proteins, labeling them for degradation by proteasomes. Impairment of the ubiquitin-proteasome system leads to the accumulation of misfolded proteins, which can contribute to the development of neurodegenerative disorders (eg, Parkinson disease).

References

- Atypical ubiquitination and Parkinson's disease.

cycle regulation, and disposal of **misfolded proteins**.

Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders

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- Atypical ubiquitination and Parkinson's disease.

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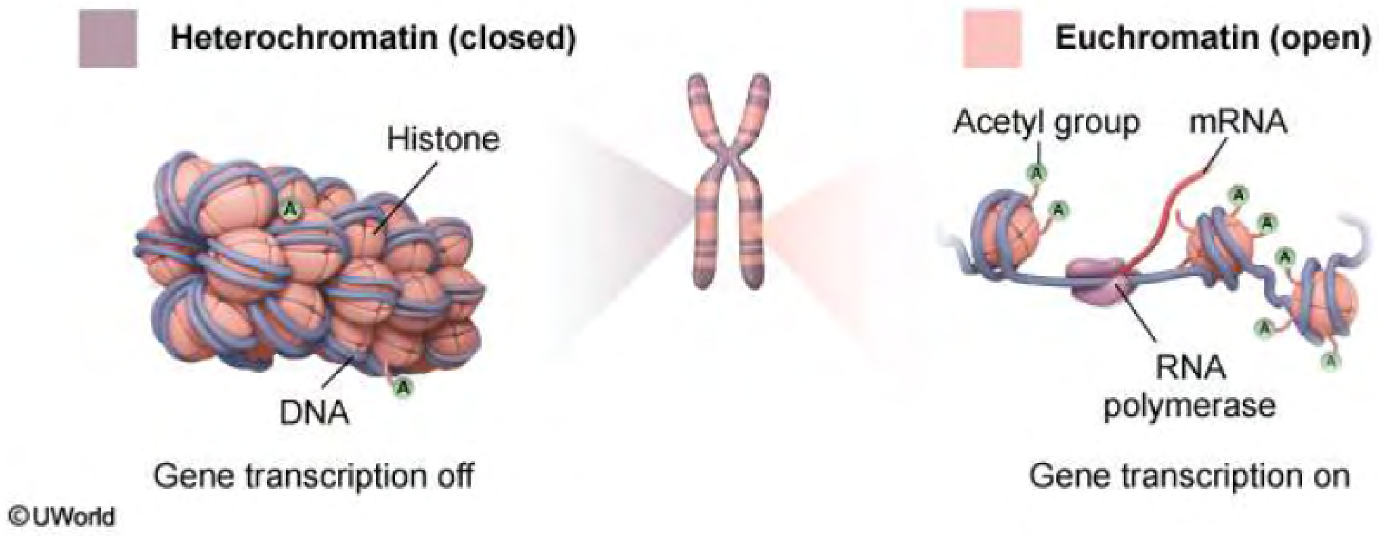
▨ Heterochromatin (closed)
Histone
DNA
A
Gene transcription off
🟥 Euchromatin (open)
Acetyl group
mRNA
A
RNA polymerase
Gene transcription on

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cycle regulation, and disposal of **misfolded proteins**.

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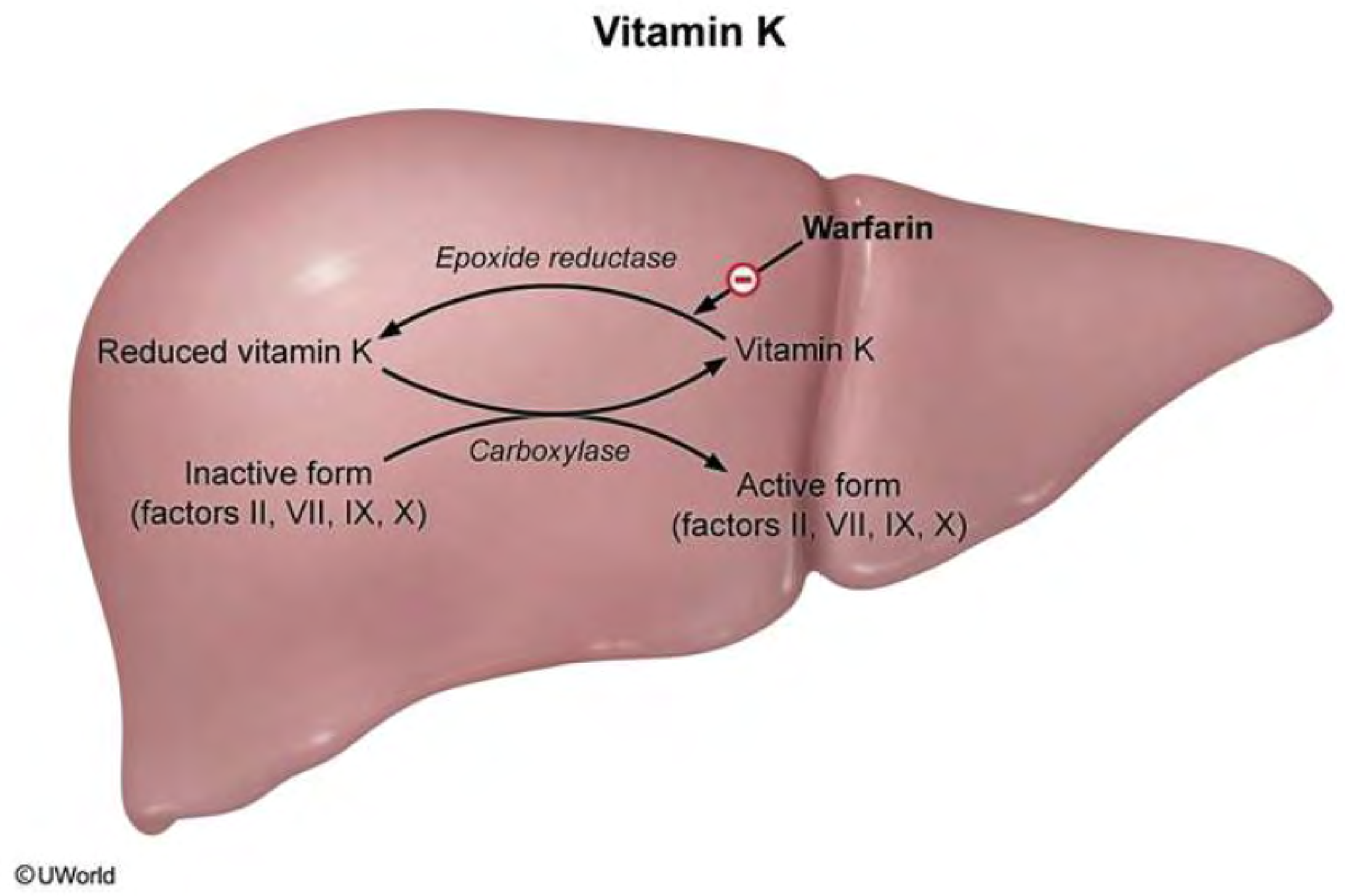
Vitamin K
Warfarin
Epoxide reductase
Reduced vitamin K
Vitamin K
Carboxylase
Inactive form
(factors II, VII, IX, X)
Active form
(factors II, VII, IX, X)
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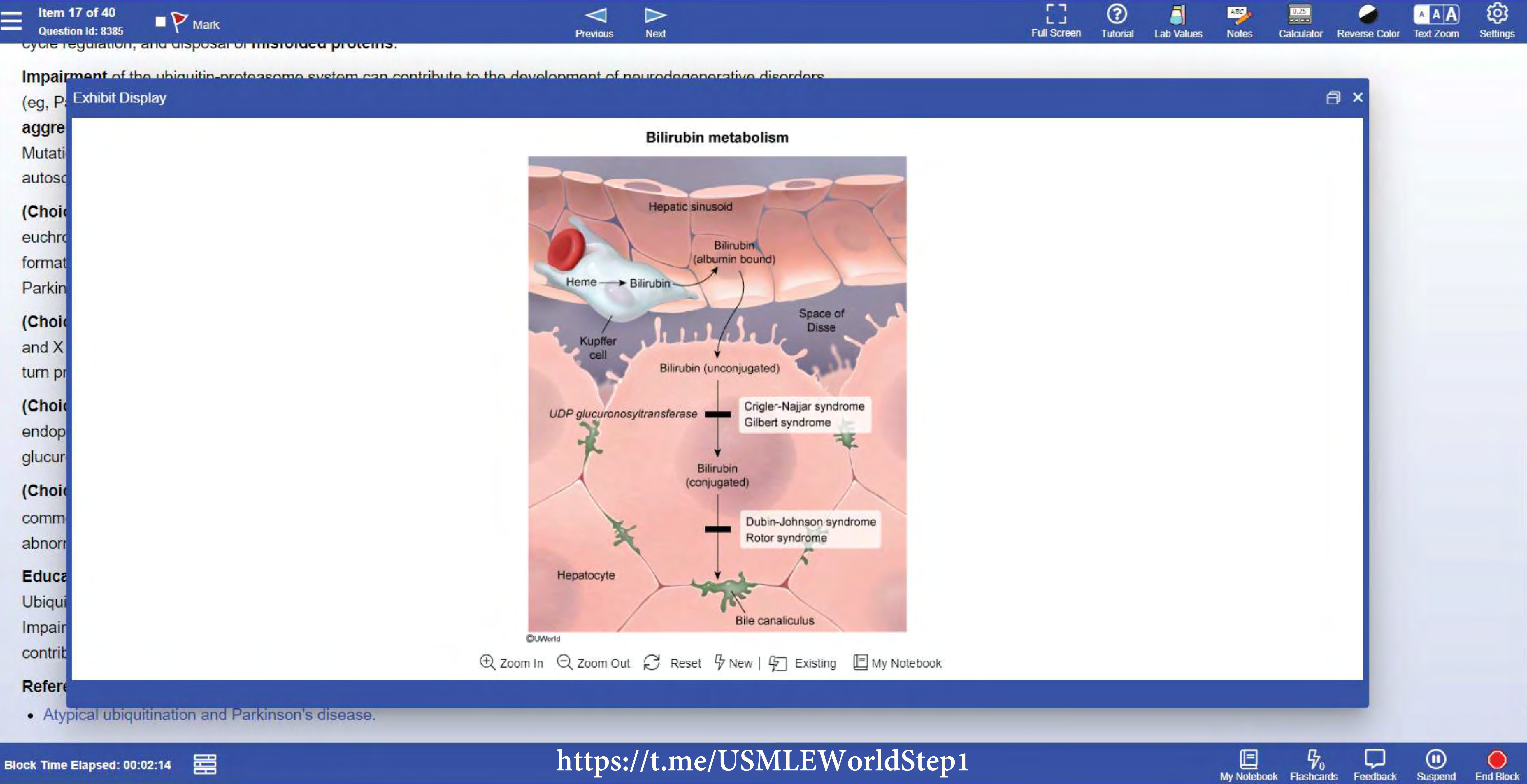
Zoom Out
Reset
New | Existing
My Notebook


Item 17 of 40
Question Id: 8385
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

cycle regulation, and disposal of **misfolded proteins**.

Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders

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Refere

- Atypical ubiquitination and Parkinson's disease.

Exhibit Display

Bilirubin metabolism

Hepatic sinusoid
Bilirubin (albumin bound)
Heme
Bilirubin
Space of Disse
Kupffer cell
Bilirubin (unconjugated)
UDP glucuronosyltransferase
Crigler-Najjar syndrome
Gilbert syndrome
Bilirubin (conjugated)
Dubin-Johnson syndrome
Rotor syndrome
Hepatocyte
Bile canaliculus

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Zoom Out
Reset
New
Existing
My Notebook

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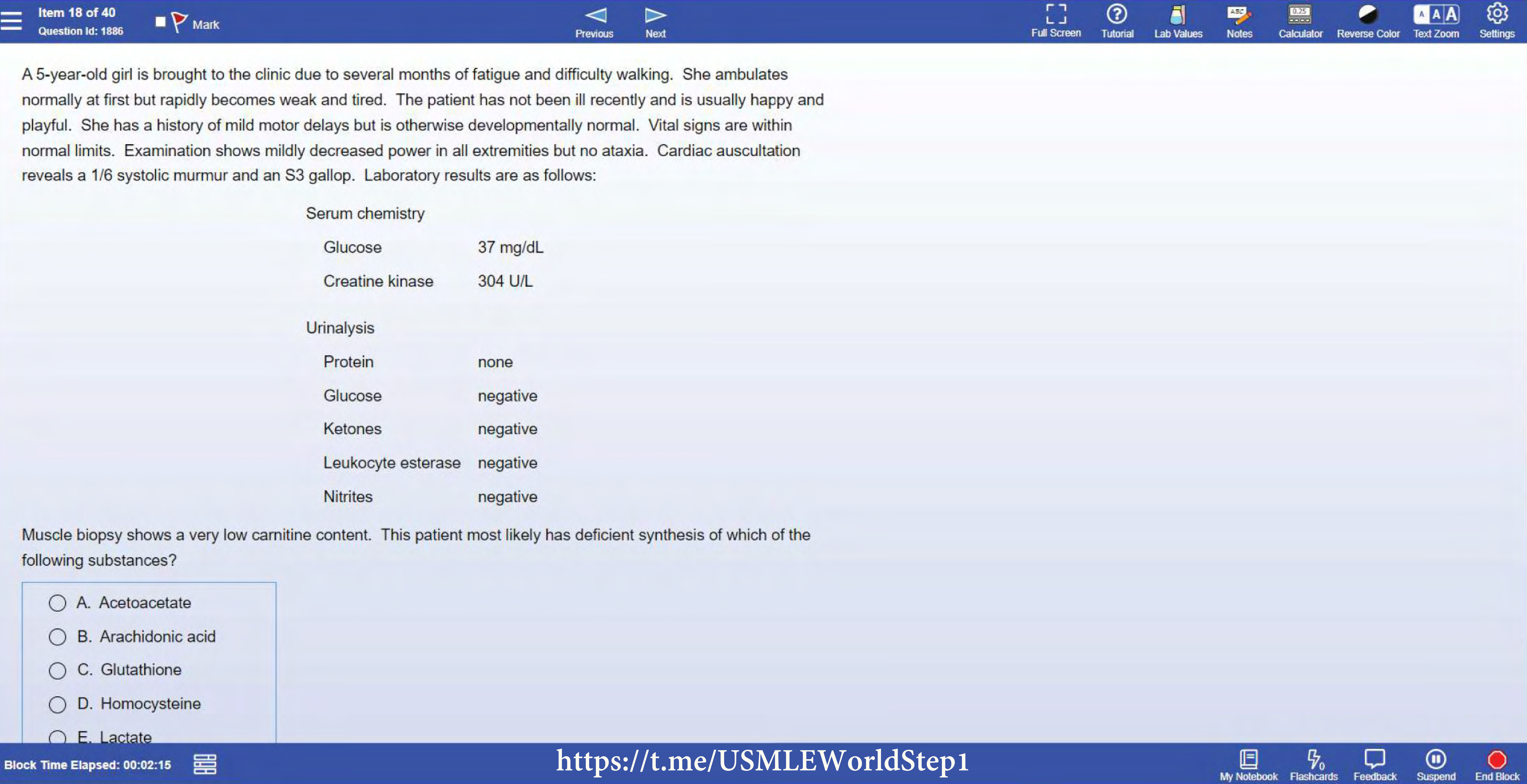
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 18 of 40
Question Id: 1886
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 5-year-old girl is brought to the clinic due to several months of fatigue and difficulty walking. She ambulates normally at first but rapidly becomes weak and tired. The patient has not been ill recently and is usually happy and playful. She has a history of mild motor delays but is otherwise developmentally normal. Vital signs are within normal limits. Examination shows mildly decreased power in all extremities but no ataxia. Cardiac auscultation reveals a 1/6 systolic murmur and an S3 gallop. Laboratory results are as follows:

Serum chemistry	
Glucose	37 mg/dL
Creatine kinase	304 U/L
Urinalysis	
Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

○ A. Acetoacetate
○ B. Arachidonic acid
○ C. Glutathione
○ D. Homocysteine
○ E. Lactate

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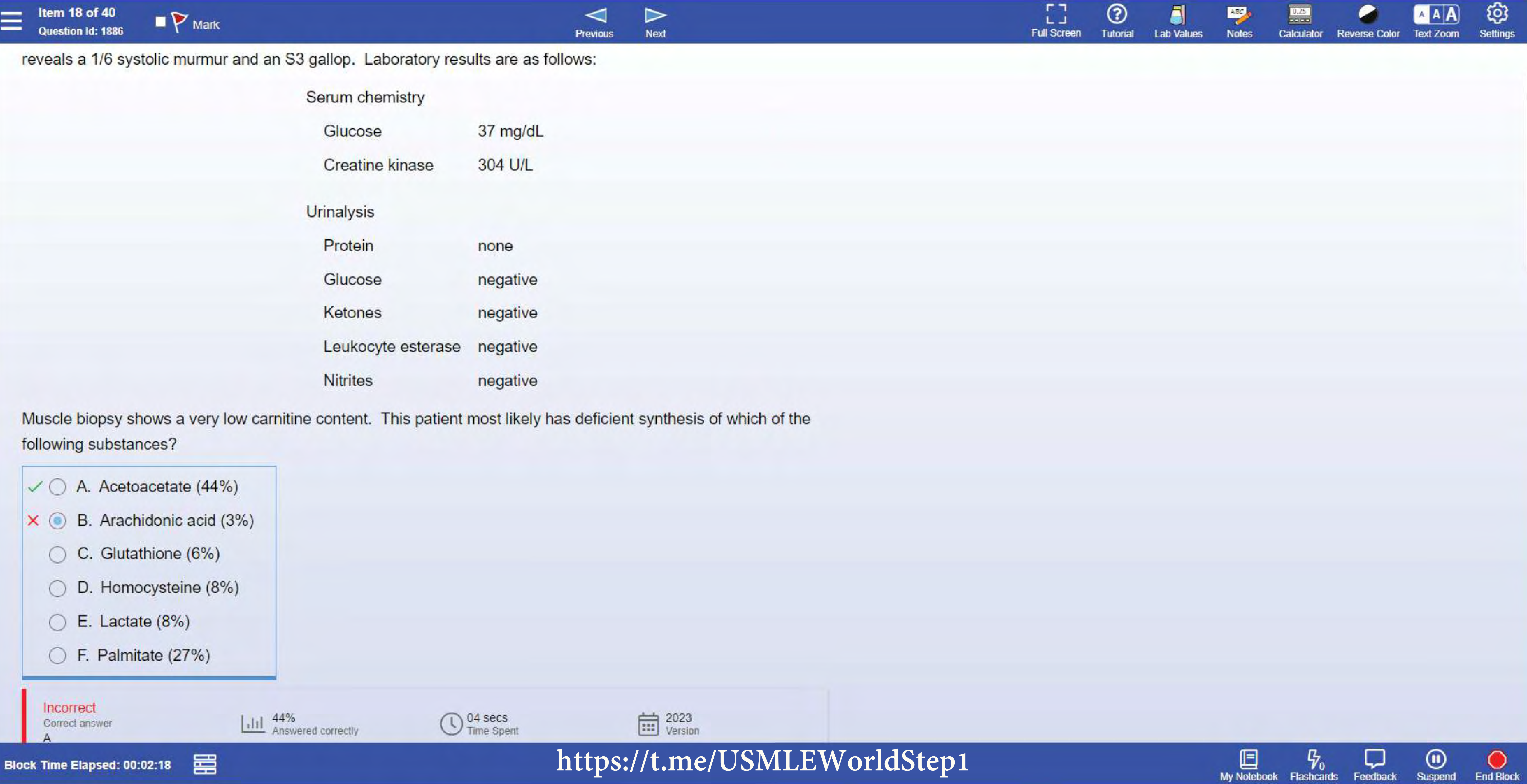
Flashcards
Feedback
Suspend
End Block


Item 18 of 40
Question Id: 1886
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Serum chemistry	
Glucose	37 mg/dL
Creatine kinase	304 U/L
Urinalysis	
Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

✓ ○ A. Acetoacetate (44%)
✗ ● B. Arachidonic acid (3%)
○ C. Glutathione (6%)
○ D. Homocysteine (8%)
○ E. Lactate (8%)
○ F. Palmitate (27%)

Incorrect
Correct answer
A

44%
Answered correctly

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2023
Version

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My Notebook
Flashcards
Feedback
Suspend
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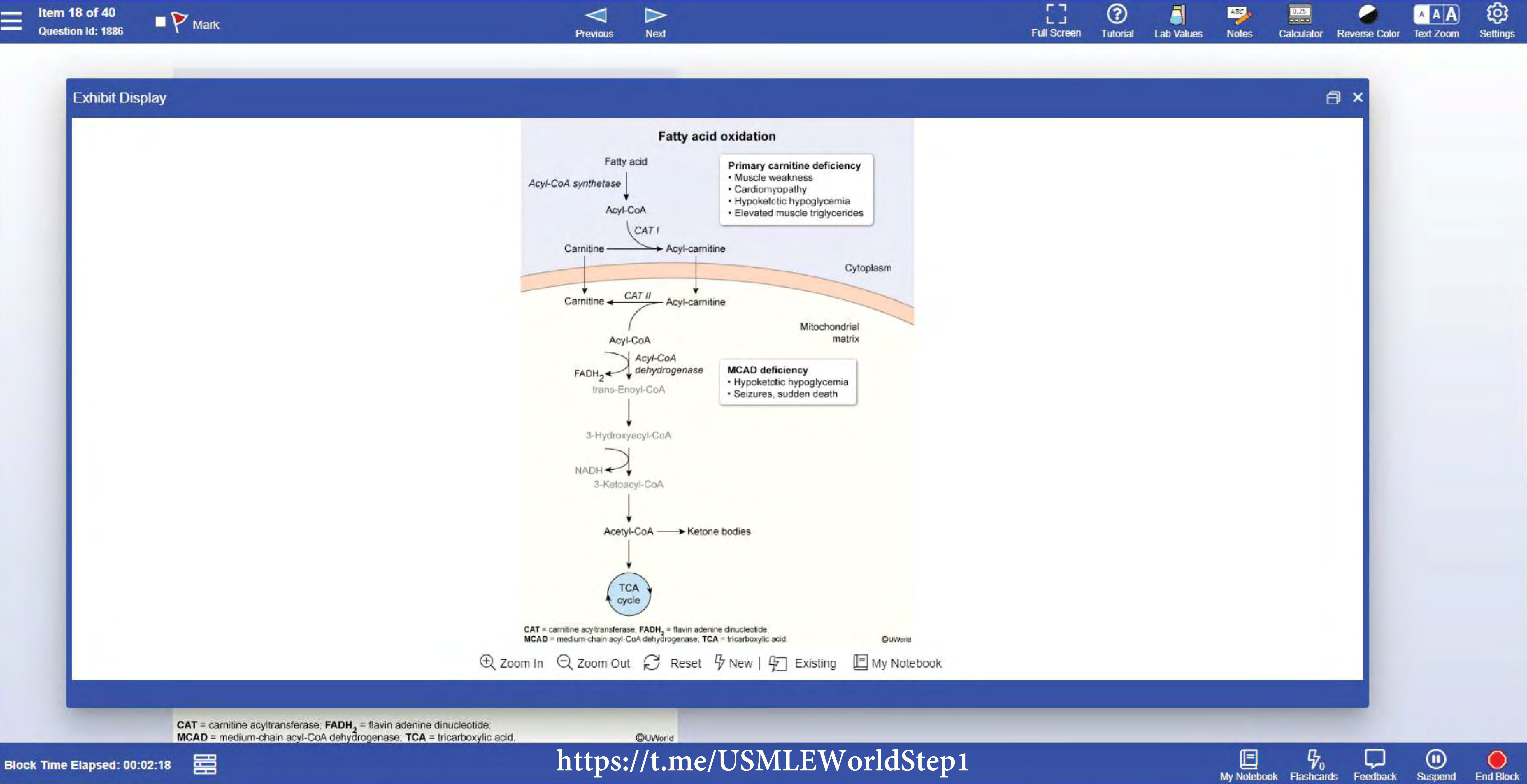
Item 18 of 40
Question Id: 1886
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display

Fatty acid oxidation

Fatty acid
Acyl-CoA synthetase
Acyl-CoA
CAT I
Carnitine
Acyl-carnitine
Cytoplasm
Carnitine
CAT II
Acyl-carnitine
Mitochondrial matrix
Acyl-CoA
Acyl-CoA dehydrogenase
FADH2
trans-Enoyl-CoA
3-Hydroxyacyl-CoA
NADH
3-Ketoacyl-CoA
Acetyl-CoA
Ketone bodies
TCA cycle

Primary carnitine deficiency

- Muscle weakness
- Cardiomyopathy
- Hypoketotic hypoglycemia
- Elevated muscle triglycerides

MCAD deficiency

- Hypoketotic hypoglycemia
- Seizures, sudden death

CAT = carnitine acyltransferase; **FADH$_2$** = flavin adenine dinucleotide; **MCAD** = medium-chain acyl-CoA dehydrogenase; **TCA** = tricarboxylic acid.

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Reset
New
Existing
My Notebook

CAT = carnitine acyltransferase; **FADH$_2$** = flavin adenine dinucleotide;
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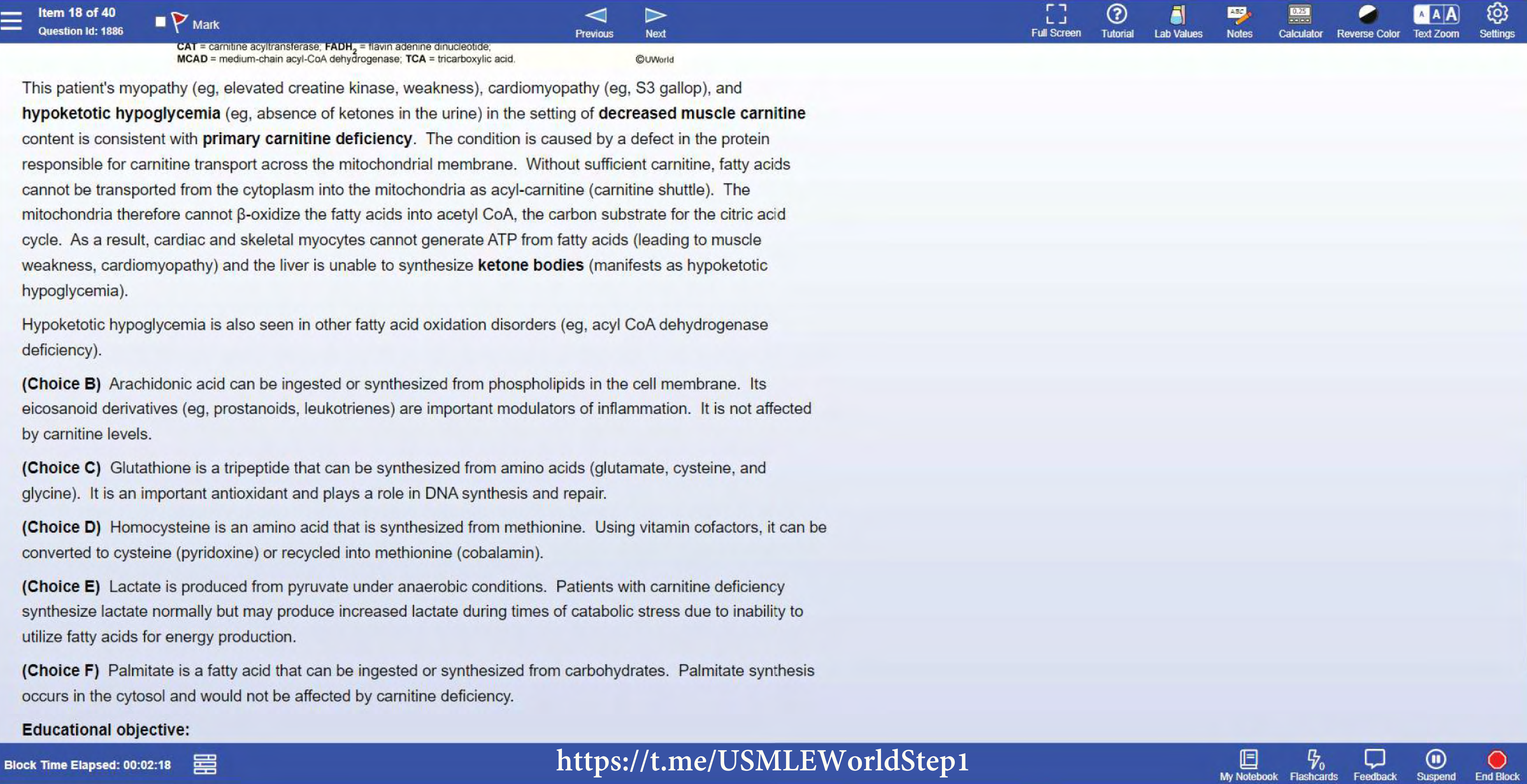
My Notebook
Flashcards
Feedback
Suspend
End Block



Item 18 of 40
Question Id: 1886

CAT = carnitine acyltransferase; **FADH$_2$** = flavin adenine dinucleotide;
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This patient's myopathy (eg, elevated creatine kinase, weakness), cardiomyopathy (eg, S3 gallop), and **hypoketotic hypoglycemia** (eg, absence of ketones in the urine) in the setting of **decreased muscle carnitine** content is consistent with **primary carnitine deficiency**. The condition is caused by a defect in the protein responsible for carnitine transport across the mitochondrial membrane. Without sufficient carnitine, fatty acids cannot be transported from the cytoplasm into the mitochondria as acyl-carnitine (carnitine shuttle). The mitochondria therefore cannot β-oxidize the fatty acids into acetyl CoA, the carbon substrate for the citric acid cycle. As a result, cardiac and skeletal myocytes cannot generate ATP from fatty acids (leading to muscle weakness, cardiomyopathy) and the liver is unable to synthesize **ketone bodies** (manifests as hypoketotic hypoglycemia).

Hypoketotic hypoglycemia is also seen in other fatty acid oxidation disorders (eg, acyl CoA dehydrogenase deficiency).

(Choice B) Arachidonic acid can be ingested or synthesized from phospholipids in the cell membrane. Its eicosanoid derivatives (eg, prostanoids, leukotrienes) are important modulators of inflammation. It is not affected by carnitine levels.

(Choice C) Glutathione is a tripeptide that can be synthesized from amino acids (glutamate, cysteine, and glycine). It is an important antioxidant and plays a role in DNA synthesis and repair.

(Choice D) Homocysteine is an amino acid that is synthesized from methionine. Using vitamin cofactors, it can be converted to cysteine (pyridoxine) or recycled into methionine (cobalamin).

(Choice E) Lactate is produced from pyruvate under anaerobic conditions. Patients with carnitine deficiency synthesize lactate normally but may produce increased lactate during times of catabolic stress due to inability to utilize fatty acids for energy production.

(Choice F) Palmitate is a fatty acid that can be ingested or synthesized from carbohydrates. Palmitate synthesis occurs in the cytosol and would not be affected by carnitine deficiency.

Educational objective:

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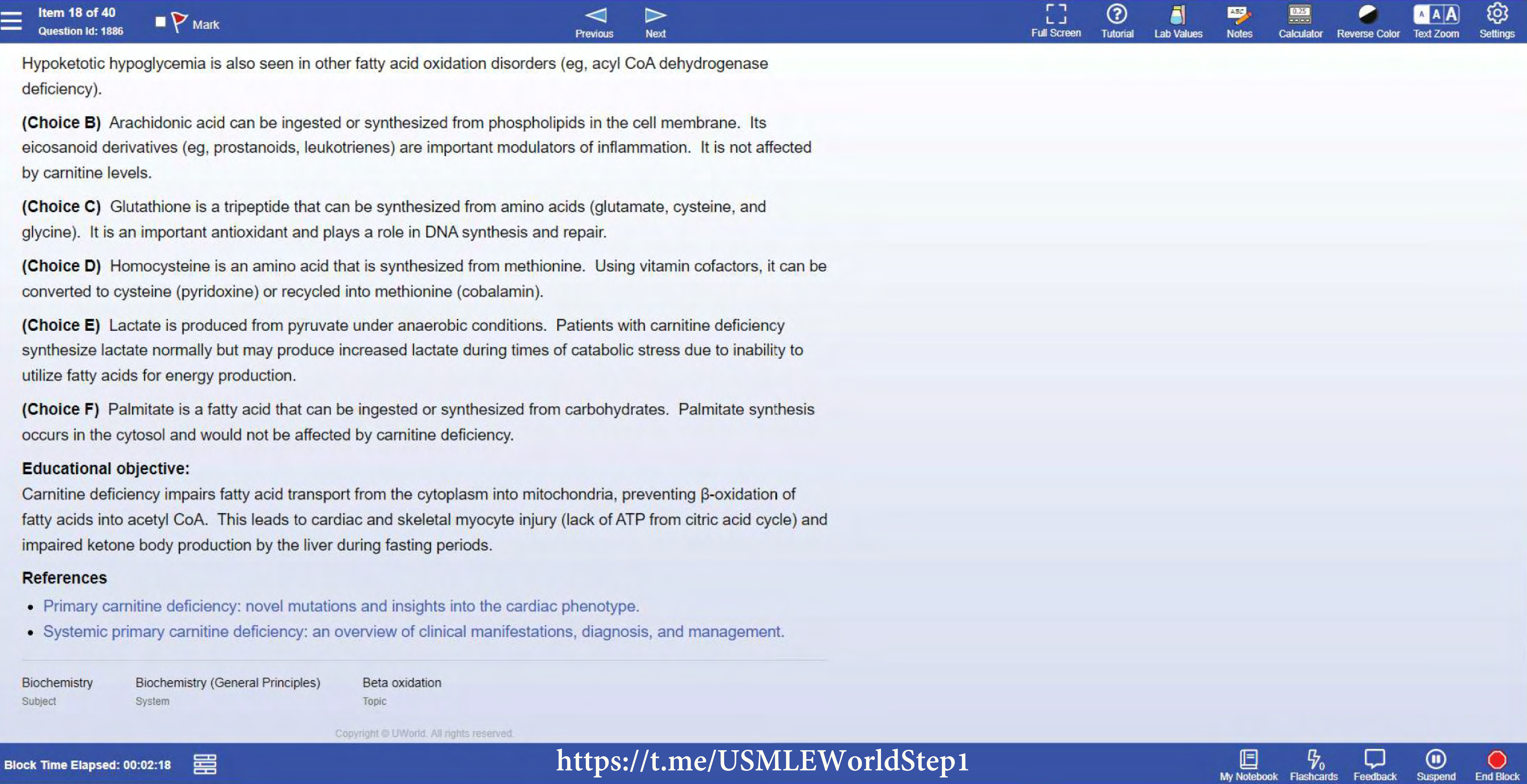
Item 18 of 40
Question Id: 1886
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choice F) Palmitate is a fatty acid that can be ingested or synthesized from carbohydrates. Palmitate synthesis occurs in the cytosol and would not be affected by carnitine deficiency.

Educational objective:

Carnitine deficiency impairs fatty acid transport from the cytoplasm into mitochondria, preventing β-oxidation of fatty acids into acetyl CoA. This leads to cardiac and skeletal myocyte injury (lack of ATP from citric acid cycle) and impaired ketone body production by the liver during fasting periods.

References

- Primary carnitine deficiency: novel mutations and insights into the cardiac phenotype.
- Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management.

Biochemistry	Biochemistry (General Principles)	Beta oxidation
Subject	System	Topic

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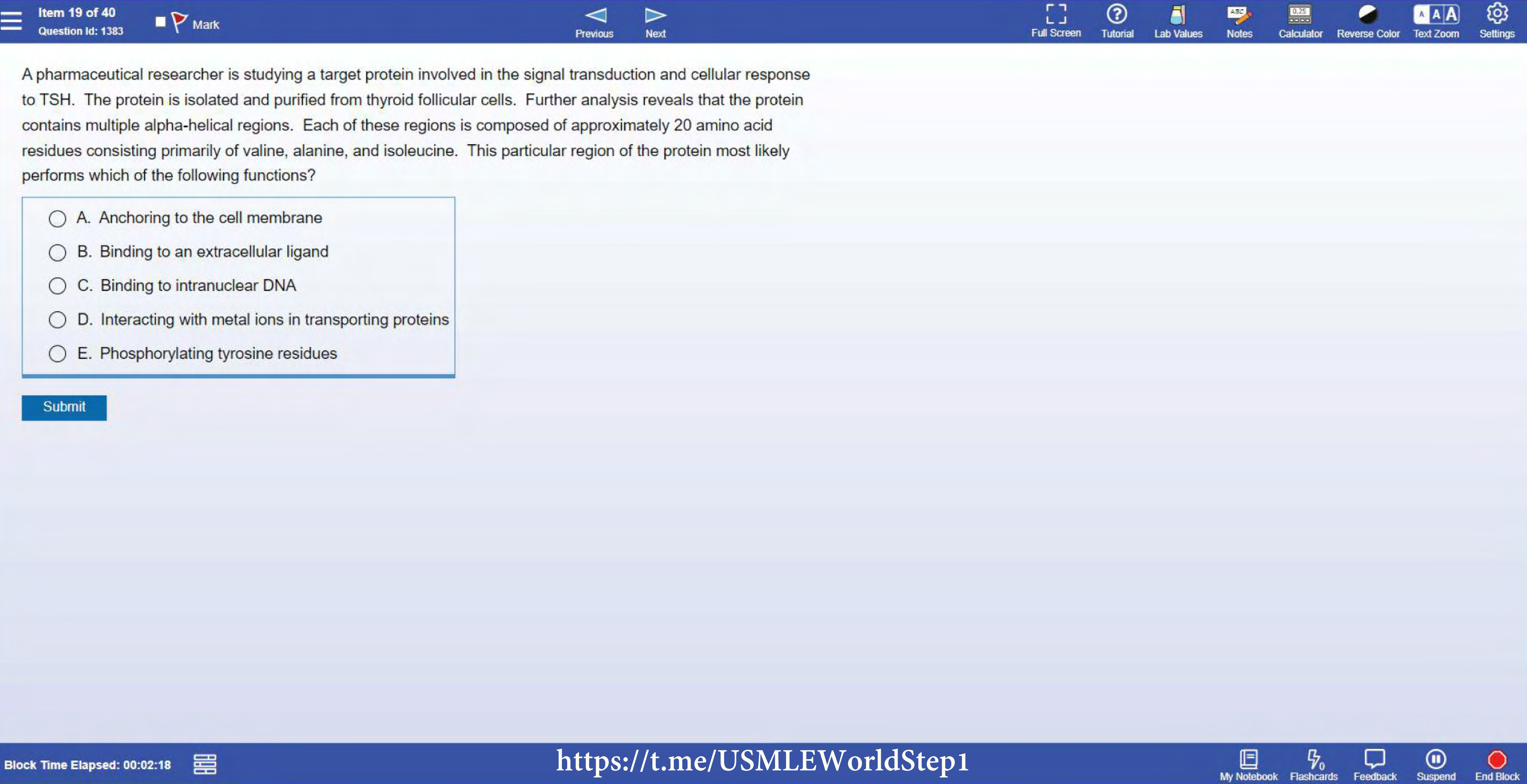
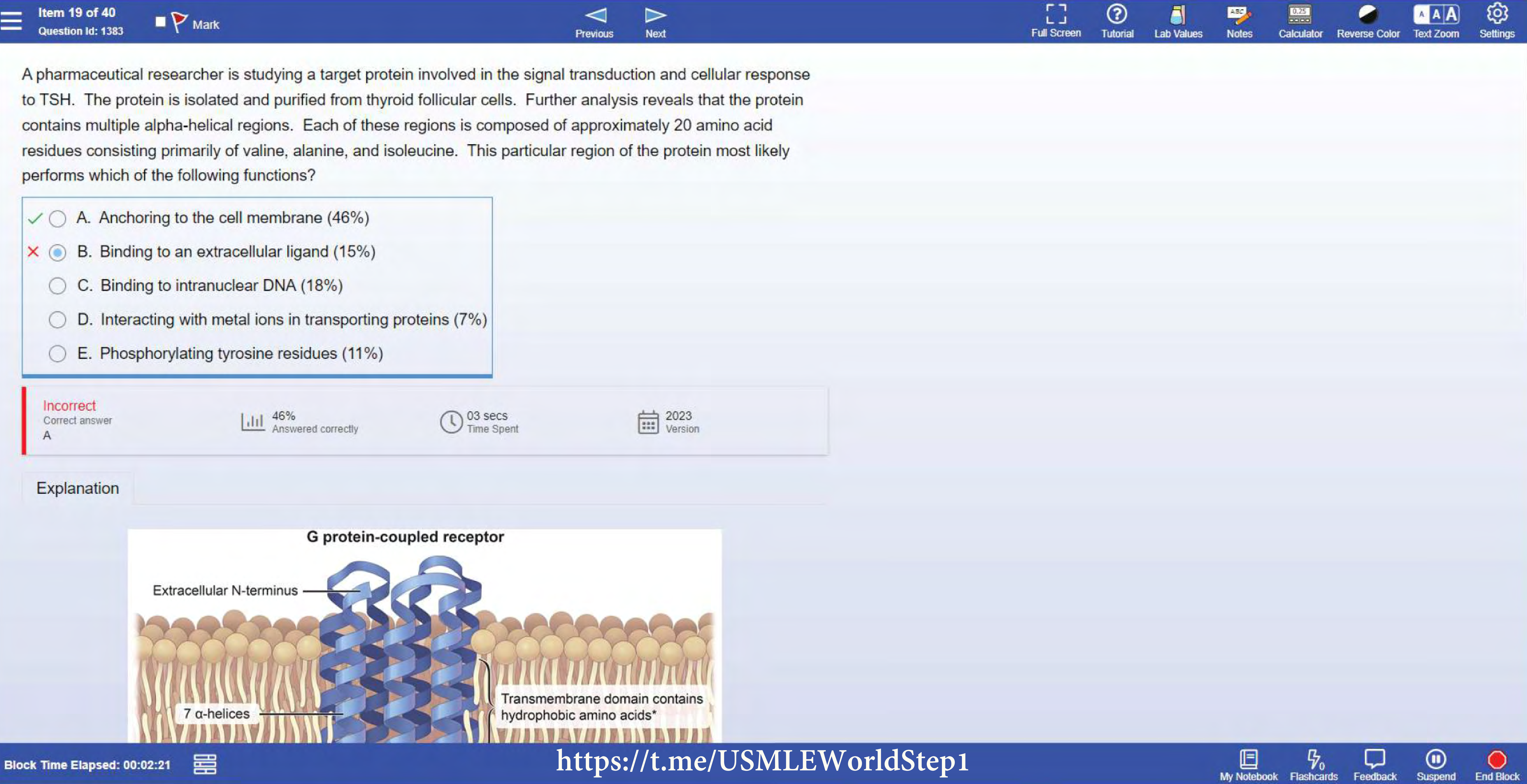
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 19 of 40
Question Id: 1383
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:02:18
My Notebook
Flashcards
Feedback
Suspend
End Block

A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

- ○ A. Anchoring to the cell membrane
- ○ B. Binding to an extracellular ligand
- ○ C. Binding to intranuclear DNA
- ○ D. Interacting with metal ions in transporting proteins
- ○ E. Phosphorylating tyrosine residues


Item 19 of 40
Question Id: 1383
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

- ✓ ○ A. Anchoring to the cell membrane (46%)
- ✗ ● B. Binding to an extracellular ligand (15%)
- ○ C. Binding to intranuclear DNA (18%)
- ○ D. Interacting with metal ions in transporting proteins (7%)
- ○ E. Phosphorylating tyrosine residues (11%)

Incorrect
Correct answer
A

46%
Answered correctly

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2023
Version

Explanation

G protein-coupled receptor

Extracellular N-terminus
7 α-helices
Transmembrane domain contains hydrophobic amino acids*

Block Time Elapsed: 00:02:21
My Notebook
Flashcards
Feedback
Suspend
End Block

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Item 19 of 40
Question Id: 1383

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Previous | Next

Full Screen | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom | Settings

Explanation

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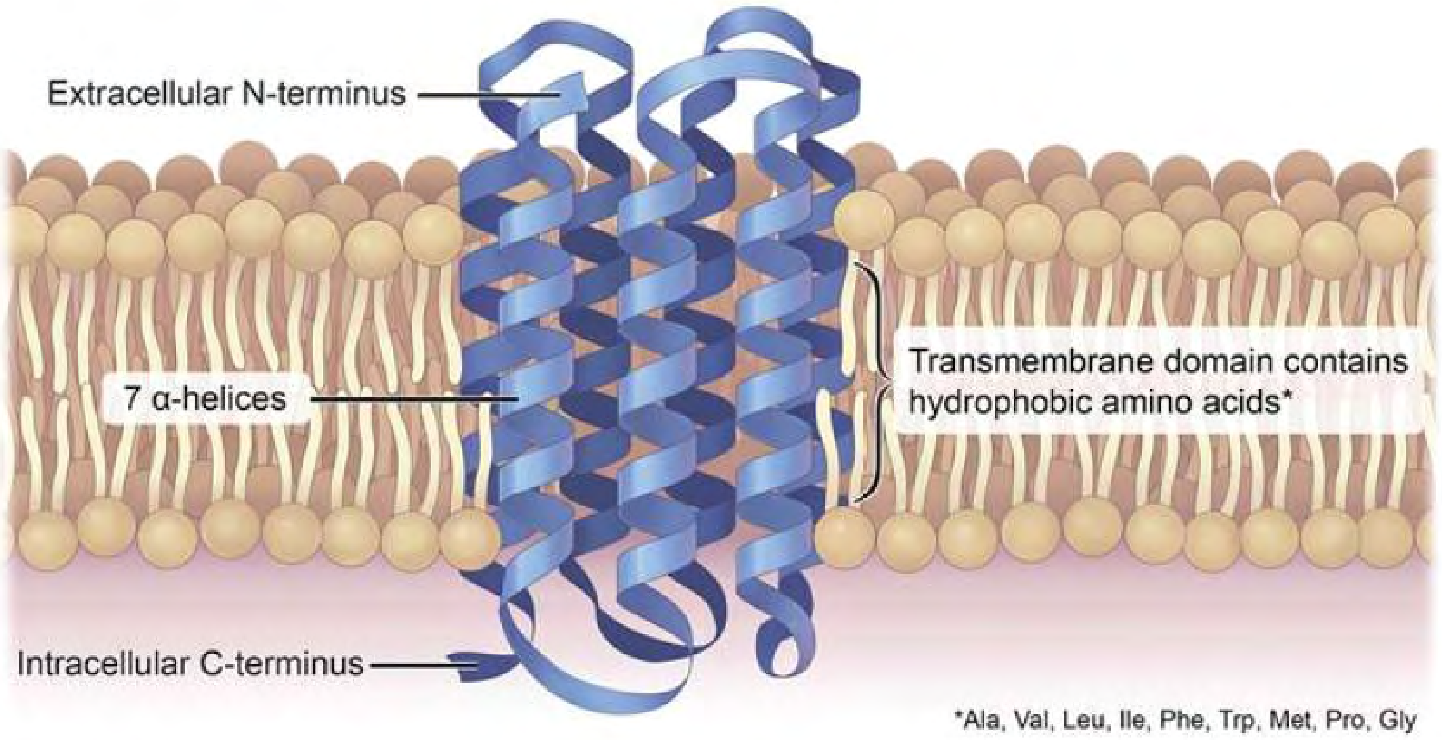
G protein-coupled receptor


Extracellular N-terminus
7 α-helices
Transmembrane domain contains hydrophobic amino acids*
Intracellular C-terminus

*Ala, Val, Leu, Ile, Phe, Trp, Met, Pro, Gly

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the cAMP or phosphatidylinositol second messenger system, activation of receptor tyrosine kinases, opening of ion

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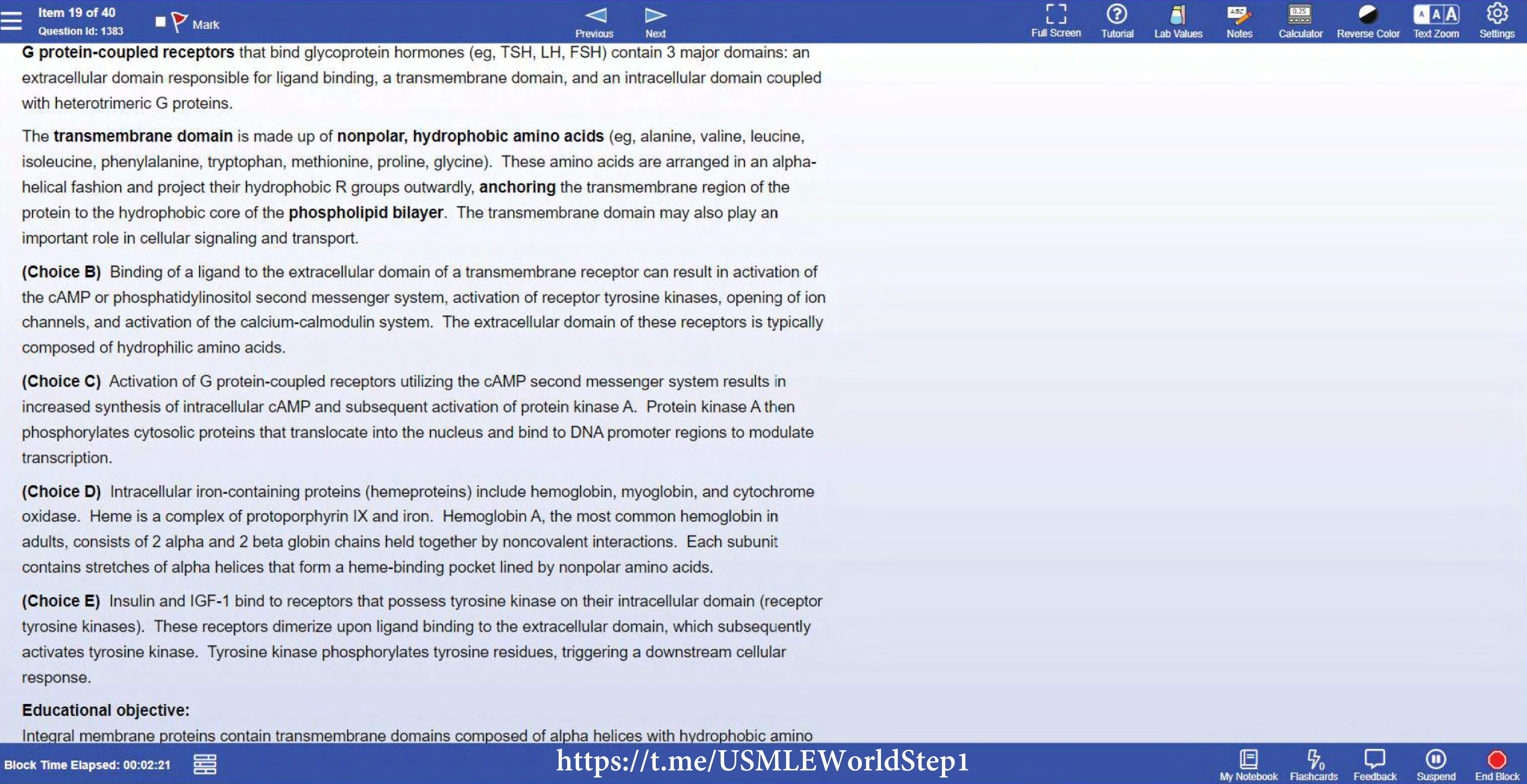


G protein-coupled receptors that bind glycoprotein hormones (eg, TSH, LH, FSH) contain 3 major domains: an extracellular domain responsible for ligand binding, a transmembrane domain, and an intracellular domain coupled with heterotrimeric G proteins.

The **transmembrane domain** is made up of **nonpolar, hydrophobic amino acids** (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups outwardly, **anchoring** the transmembrane region of the protein to the hydrophobic core of the **phospholipid bilayer**. The transmembrane domain may also play an important role in cellular signaling and transport.

(Choice B) Binding of a ligand to the extracellular domain of a transmembrane receptor can result in activation of the cAMP or phosphatidylinositol second messenger system, activation of receptor tyrosine kinases, opening of ion channels, and activation of the calcium-calmodulin system. The extracellular domain of these receptors is typically composed of hydrophilic amino acids.

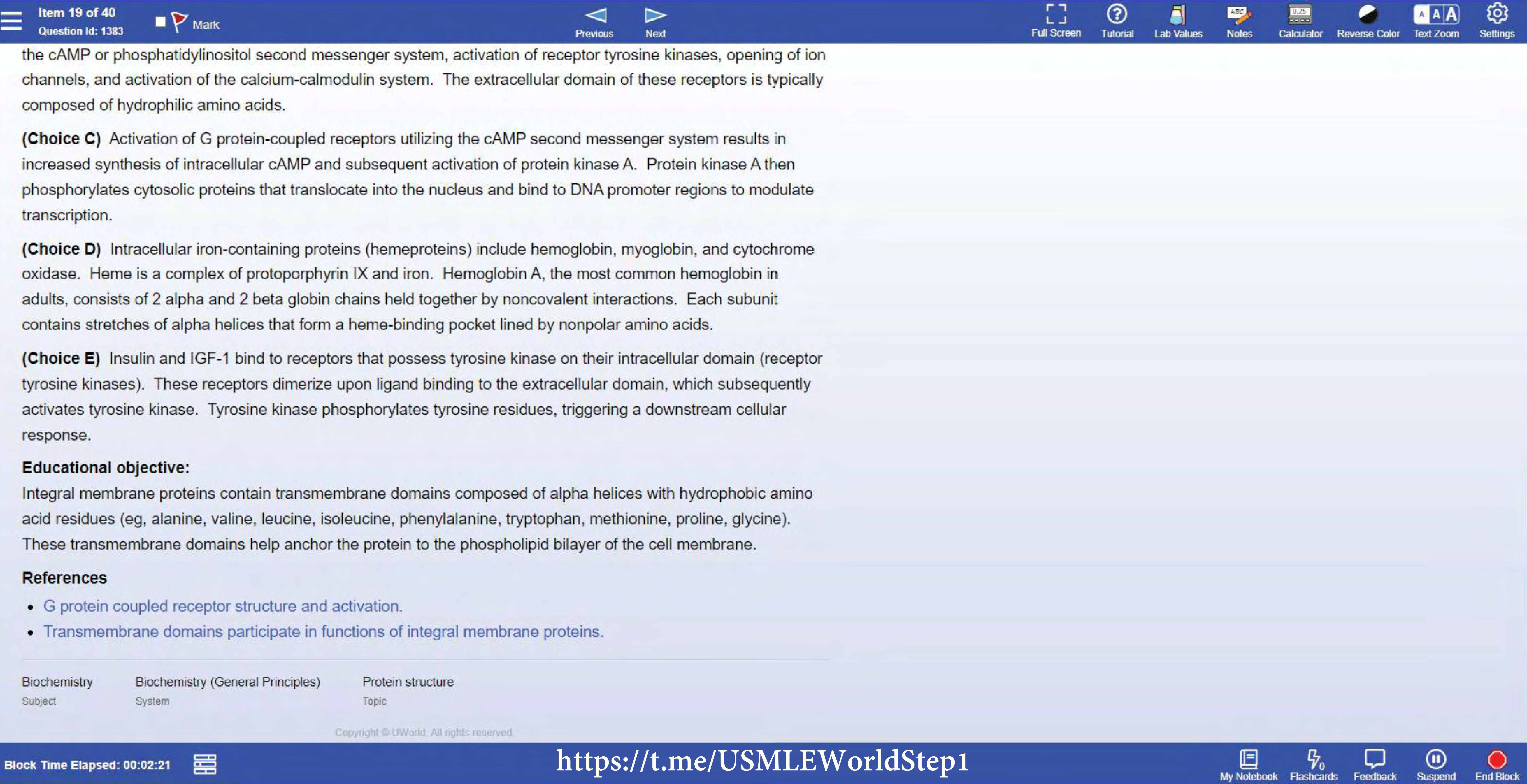
(Choice C) Activation of G protein-coupled receptors utilizing the cAMP second messenger system results in increased synthesis of intracellular cAMP and subsequent activation of protein kinase A. Protein kinase A then phosphorylates cytosolic proteins that translocate into the nucleus and bind to DNA promoter regions to modulate transcription.

(Choice D) Intracellular iron-containing proteins (hemeproteins) include hemoglobin, myoglobin, and cytochrome oxidase. Heme is a complex of protoporphyrin IX and iron. Hemoglobin A, the most common hemoglobin in adults, consists of 2 alpha and 2 beta globin chains held together by noncovalent interactions. Each subunit contains stretches of alpha helices that form a heme-binding pocket lined by nonpolar amino acids.

(Choice E) Insulin and IGF-1 bind to receptors that possess tyrosine kinase on their intracellular domain (receptor tyrosine kinases). These receptors dimerize upon ligand binding to the extracellular domain, which subsequently activates tyrosine kinase. Tyrosine kinase phosphorylates tyrosine residues, triggering a downstream cellular response.

Educational objective:

Integral membrane proteins contain transmembrane domains composed of alpha helices with hydrophobic amino



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Educational objective:

Integral membrane proteins contain transmembrane domains composed of alpha helices with hydrophobic amino acid residues (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These transmembrane domains help anchor the protein to the phospholipid bilayer of the cell membrane.

References

- G protein coupled receptor structure and activation.
- Transmembrane domains participate in functions of integral membrane proteins.

Biochemistry	Biochemistry (General Principles)	Protein structure
Subject	System	Topic

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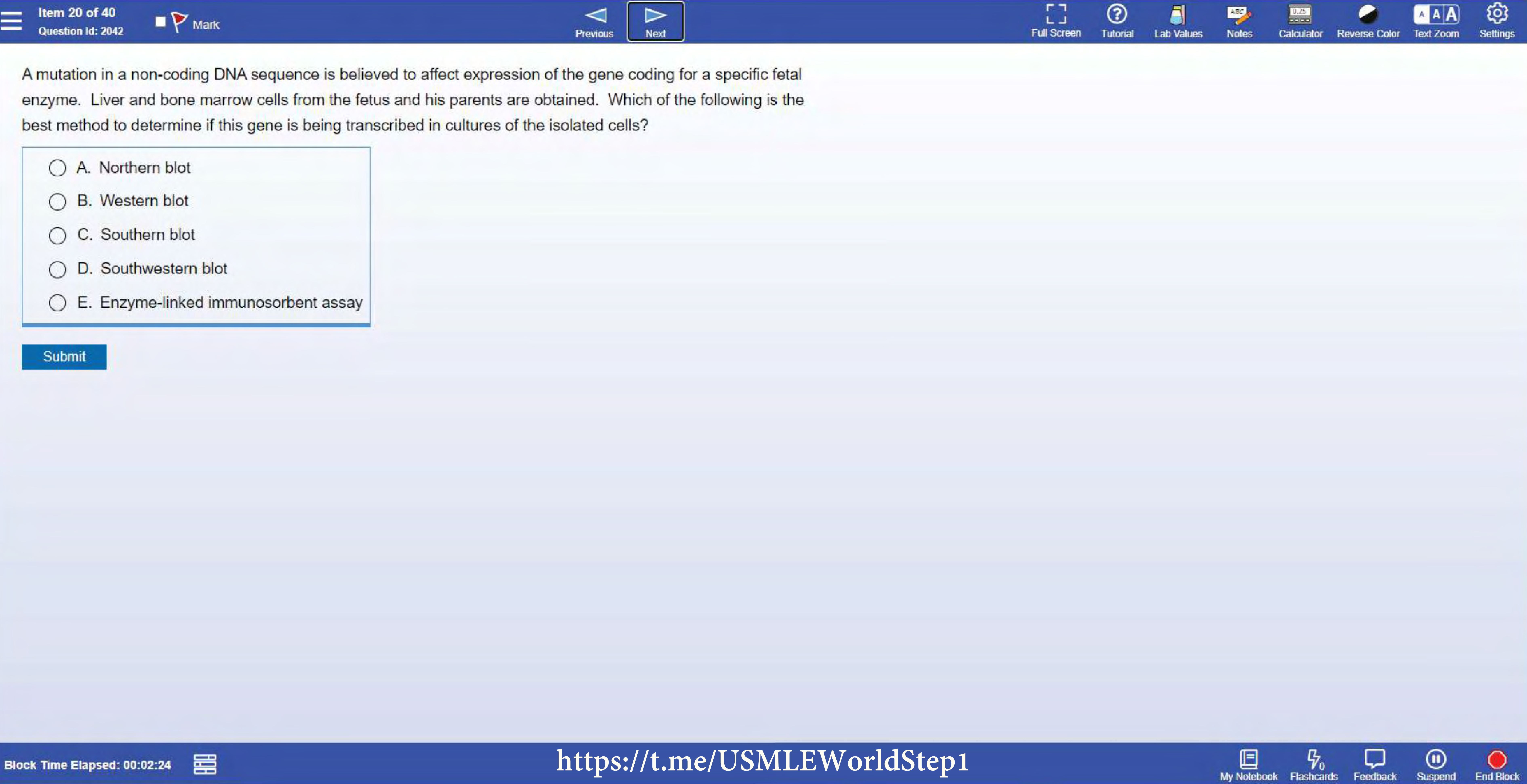
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 20 of 40
Question Id: 2042

A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

○ A. Northern blot
○ B. Western blot
○ C. Southern blot
○ D. Southwestern blot
○ E. Enzyme-linked immunosorbent assay

Submit

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A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

- ✓ ○ A. Northern blot (46%)
- ✗ ● B. Western blot (16%)
- ○ C. Southern blot (27%)
- ○ D. Southwestern blot (4%)
- ○ E. Enzyme-linked immunosorbent assay (5%)

Incorrect
Correct answer
A

46%
Answered correctly

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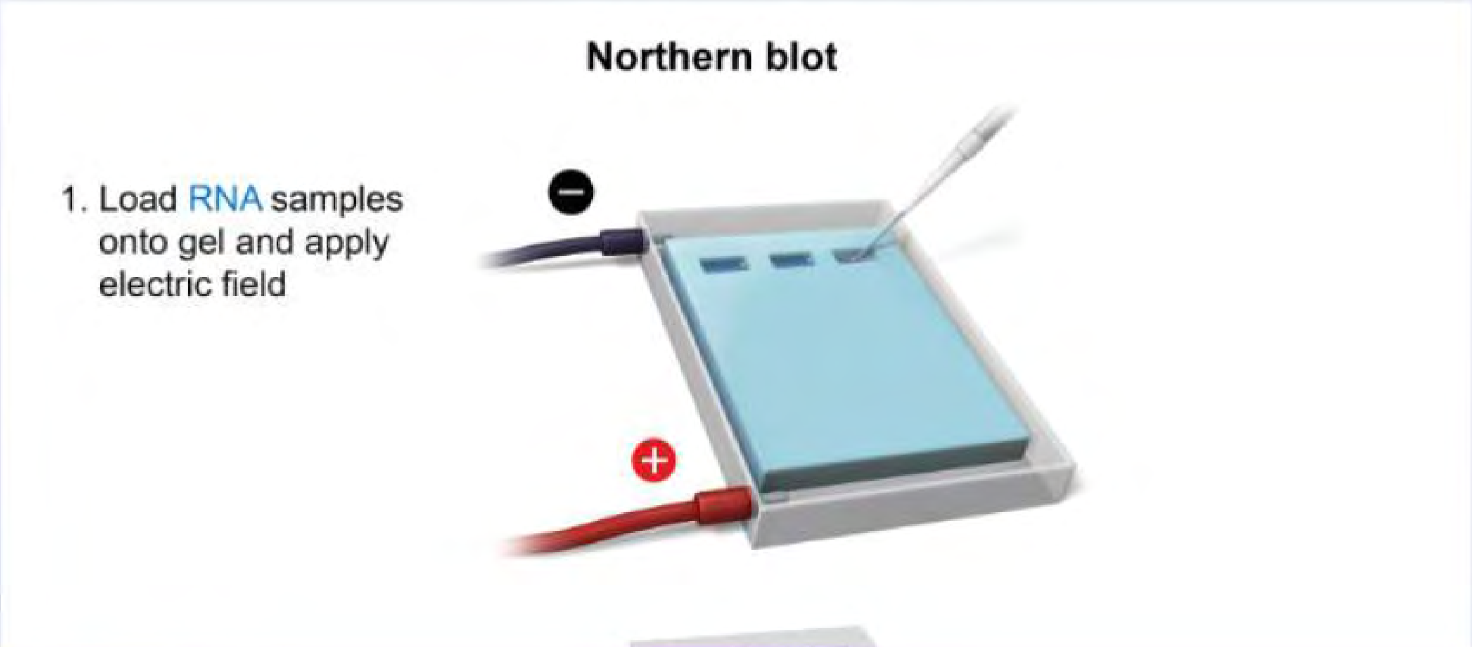
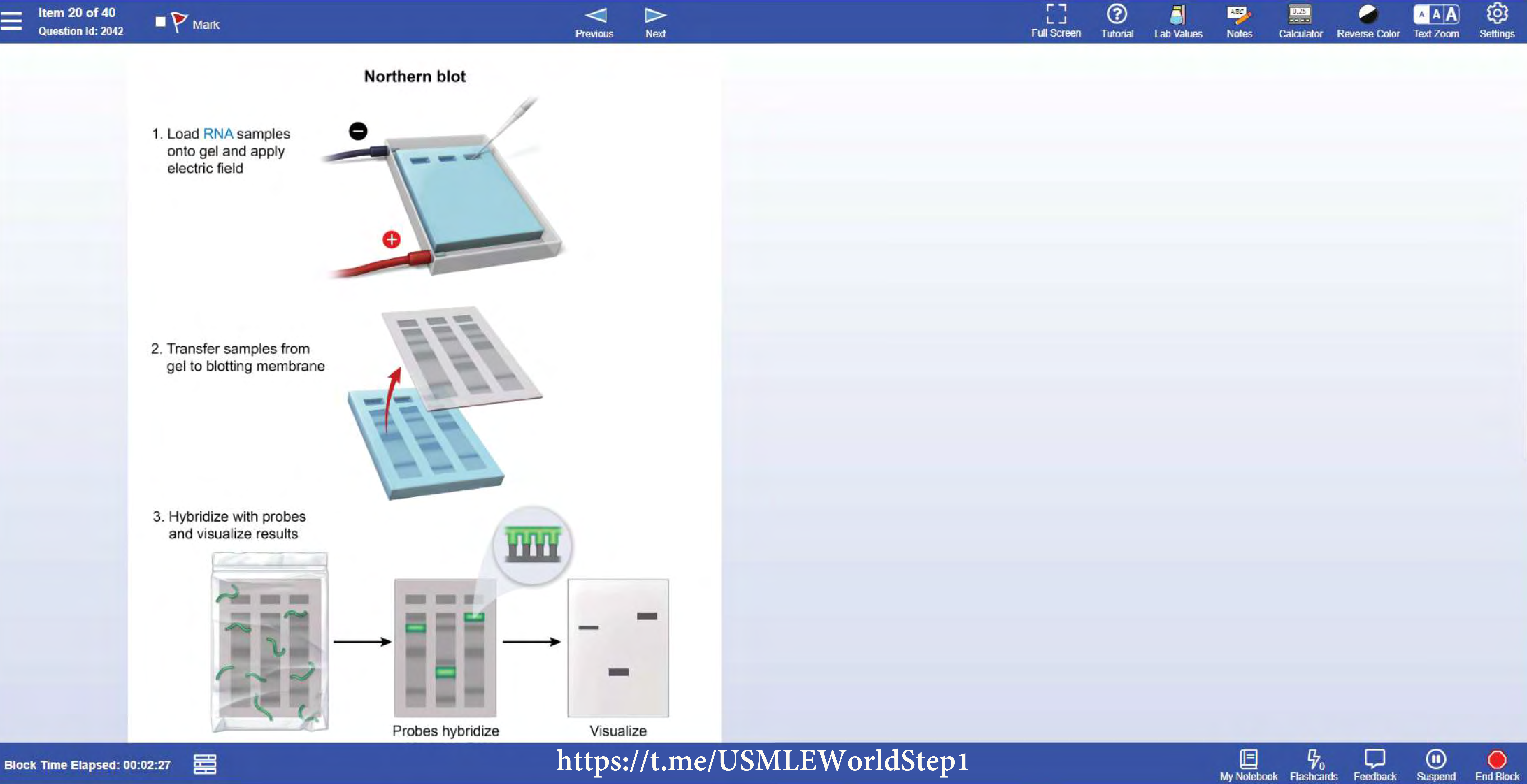
2023
Version

Explanation



Northern blot

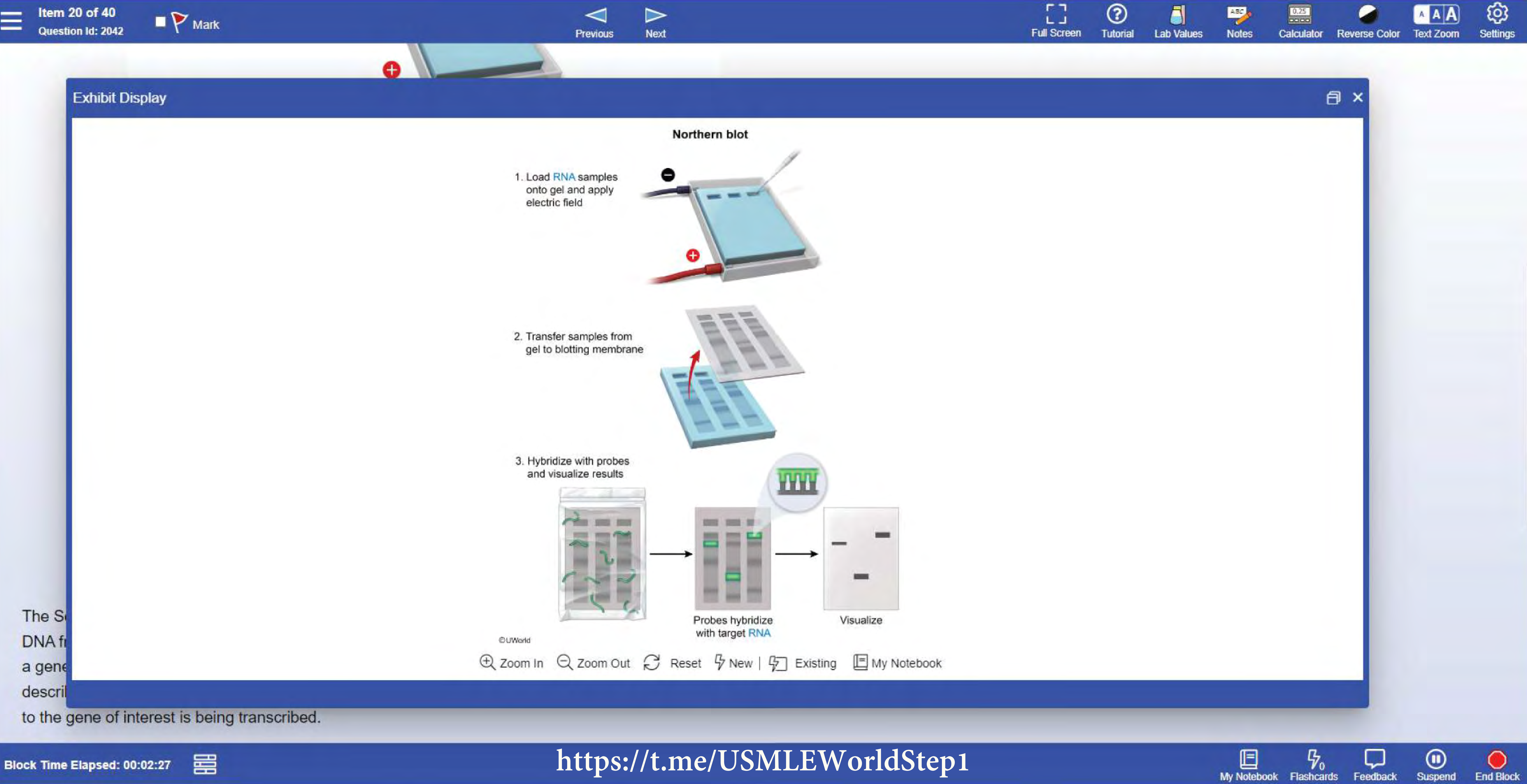
1. Load RNA samples onto gel and apply electric field


Item 20 of 40
Question Id: 2042
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Northern blot

1. Load RNA samples onto gel and apply electric field
2. Transfer samples from gel to blotting membrane
3. Hybridize with probes and visualize results

Probes hybridize
Visualize
Block Time Elapsed: 00:02:27
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 20 of 40
Question Id: 2042
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display

Northern blot

1. Load RNA samples onto gel and apply electric field

2. Transfer samples from gel to blotting membrane

3. Hybridize with probes and visualize results

Probes hybridize with target RNA
Visualize
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Zoom Out
Reset
New
Existing
My Notebook

The S
DNA fr
a gene
descri
to the gene of interest is being transcribed.

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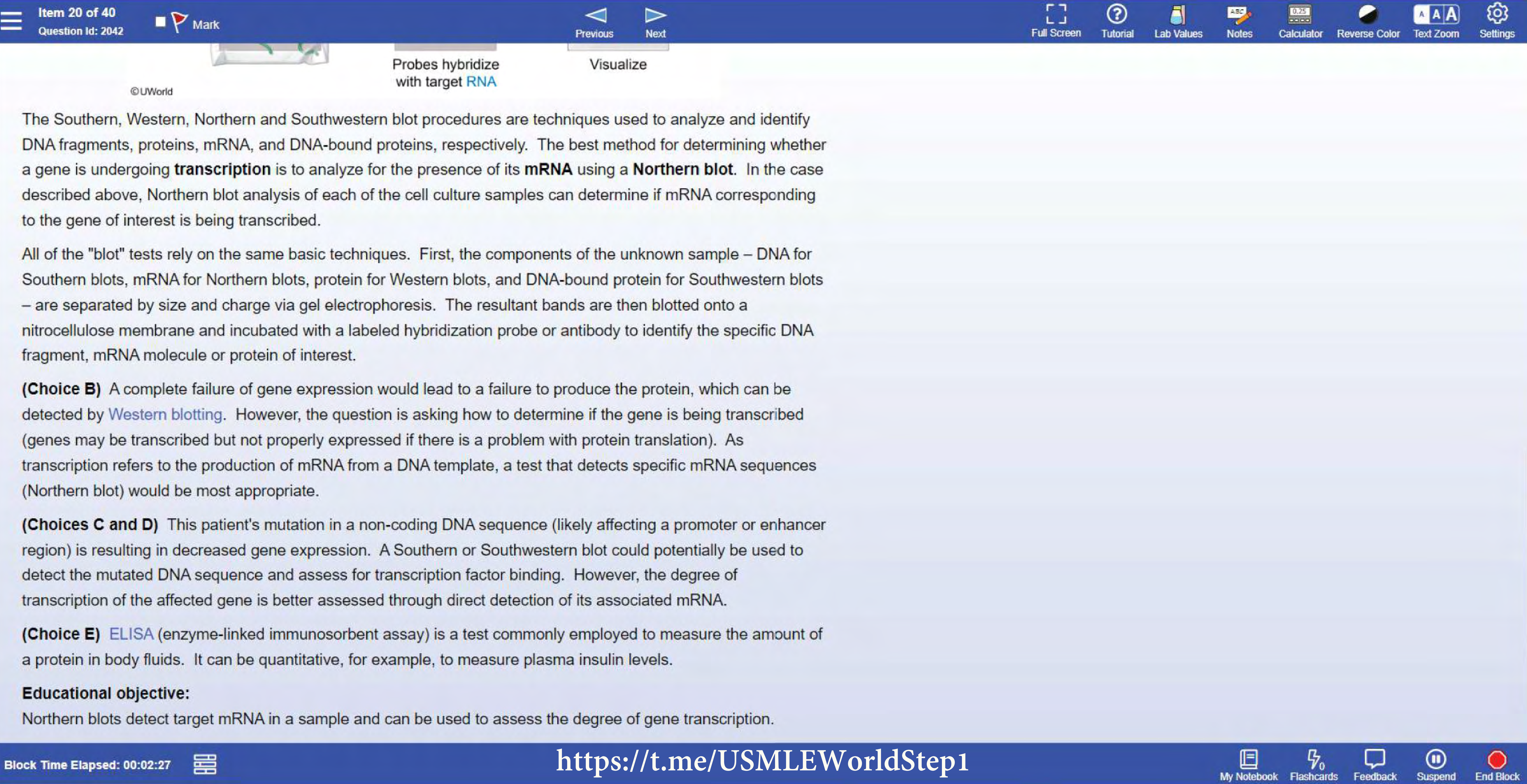
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 20 of 40
Question Id: 2042
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Probes hybridize with target RNA
Visualize
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Block Time Elapsed: 00:02:27
My Notebook
Flashcards
Feedback
Suspend
End Block

The Southern, Western, Northern and Southwestern blot procedures are techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The best method for determining whether a gene is undergoing **transcription** is to analyze for the presence of its **mRNA** using a **Northern blot**. In the case described above, Northern blot analysis of each of the cell culture samples can determine if mRNA corresponding to the gene of interest is being transcribed.

All of the "blot" tests rely on the same basic techniques. First, the components of the unknown sample – DNA for Southern blots, mRNA for Northern blots, protein for Western blots, and DNA-bound protein for Southwestern blots – are separated by size and charge via gel electrophoresis. The resultant bands are then blotted onto a nitrocellulose membrane and incubated with a labeled hybridization probe or antibody to identify the specific DNA fragment, mRNA molecule or protein of interest.

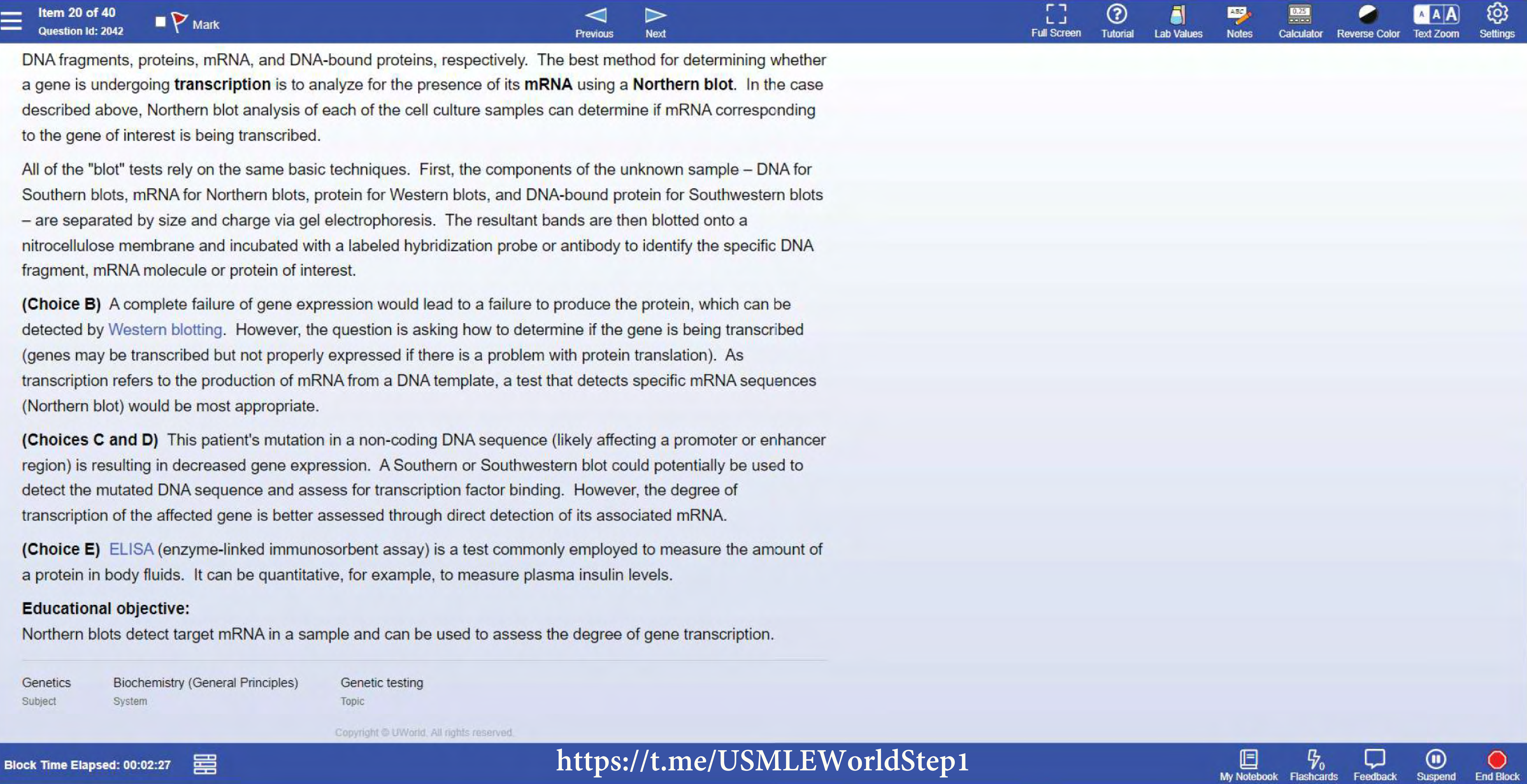
(Choice B) A complete failure of gene expression would lead to a failure to produce the protein, which can be detected by Western blotting. However, the question is asking how to determine if the gene is being transcribed (genes may be transcribed but not properly expressed if there is a problem with protein translation). As transcription refers to the production of mRNA from a DNA template, a test that detects specific mRNA sequences (Northern blot) would be most appropriate.

(Choices C and D) This patient's mutation in a non-coding DNA sequence (likely affecting a promoter or enhancer region) is resulting in decreased gene expression. A Southern or Southwestern blot could potentially be used to detect the mutated DNA sequence and assess for transcription factor binding. However, the degree of transcription of the affected gene is better assessed through direct detection of its associated mRNA.

(Choice E) ELISA (enzyme-linked immunosorbent assay) is a test commonly employed to measure the amount of a protein in body fluids. It can be quantitative, for example, to measure plasma insulin levels.

Educational objective:

Northern blots detect target mRNA in a sample and can be used to assess the degree of gene transcription.



DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The best method for determining whether a gene is undergoing **transcription** is to analyze for the presence of its **mRNA** using a **Northern blot**. In the case described above, Northern blot analysis of each of the cell culture samples can determine if mRNA corresponding to the gene of interest is being transcribed.

All of the "blot" tests rely on the same basic techniques. First, the components of the unknown sample – DNA for Southern blots, mRNA for Northern blots, protein for Western blots, and DNA-bound protein for Southwestern blots – are separated by size and charge via gel electrophoresis. The resultant bands are then blotted onto a nitrocellulose membrane and incubated with a labeled hybridization probe or antibody to identify the specific DNA fragment, mRNA molecule or protein of interest.

(Choice B) A complete failure of gene expression would lead to a failure to produce the protein, which can be detected by Western blotting. However, the question is asking how to determine if the gene is being transcribed (genes may be transcribed but not properly expressed if there is a problem with protein translation). As transcription refers to the production of mRNA from a DNA template, a test that detects specific mRNA sequences (Northern blot) would be most appropriate.

(Choices C and D) This patient's mutation in a non-coding DNA sequence (likely affecting a promoter or enhancer region) is resulting in decreased gene expression. A Southern or Southwestern blot could potentially be used to detect the mutated DNA sequence and assess for transcription factor binding. However, the degree of transcription of the affected gene is better assessed through direct detection of its associated mRNA.

(Choice E) ELISA (enzyme-linked immunosorbent assay) is a test commonly employed to measure the amount of a protein in body fluids. It can be quantitative, for example, to measure plasma insulin levels.

Educational objective:

Northern blots detect target mRNA in a sample and can be used to assess the degree of gene transcription.

Genetics	Biochemistry (General Principles)	Genetic testing
Subject	System	Topic

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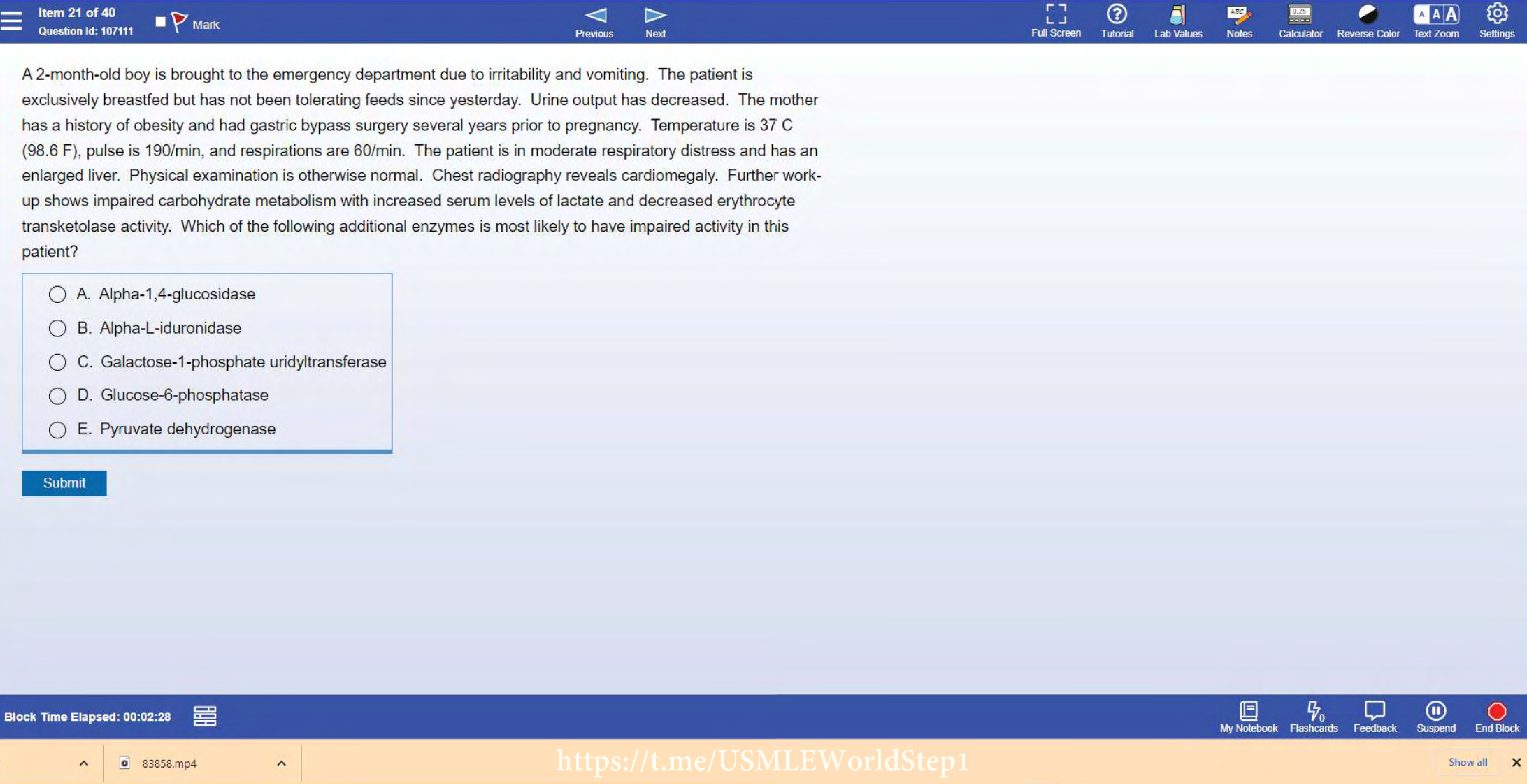
Item 21 of 40
Question Id: 107111
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
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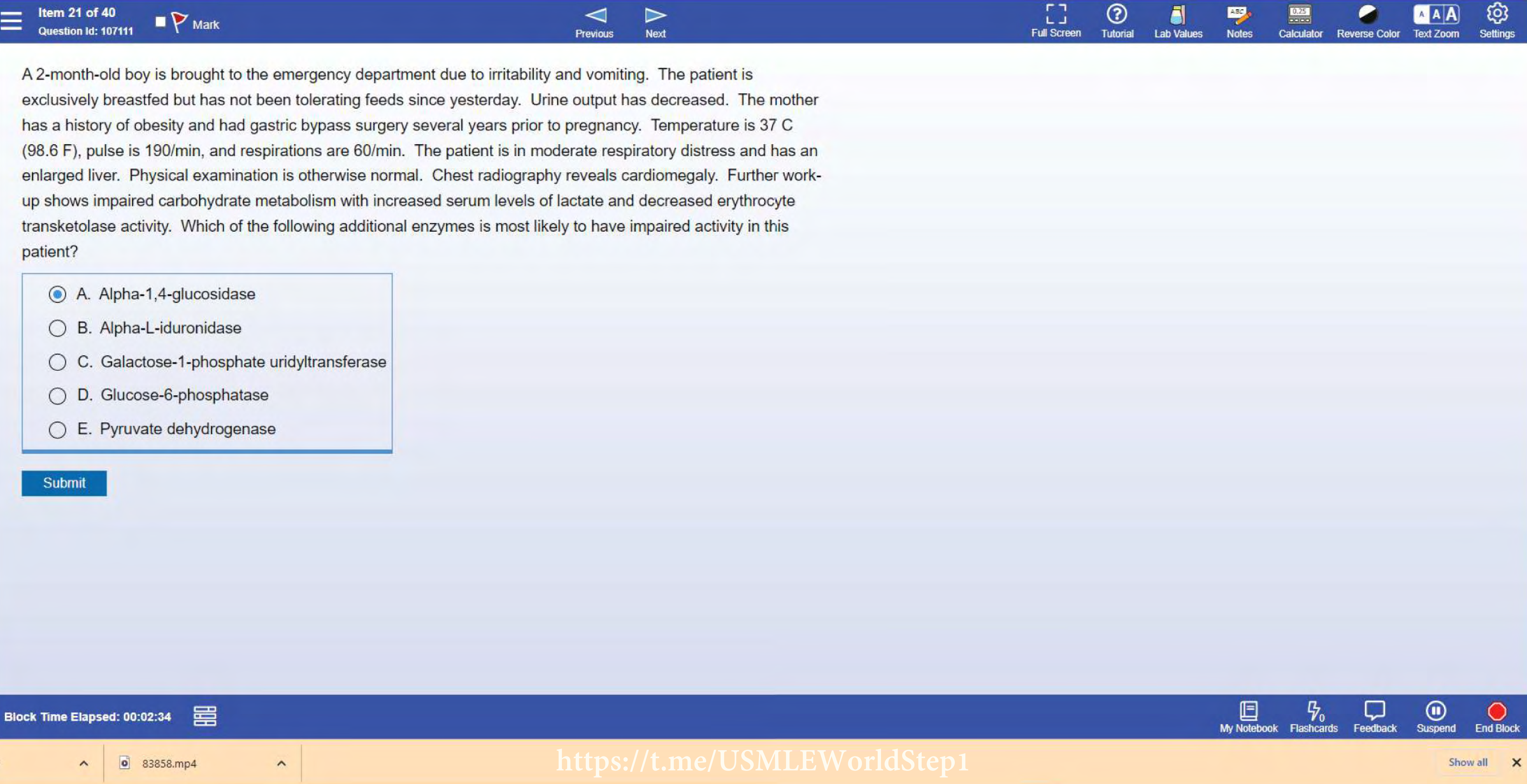
A 2-month-old boy is brought to the emergency department due to irritability and vomiting. The patient is exclusively breastfed but has not been tolerating feeds since yesterday. Urine output has decreased. The mother has a history of obesity and had gastric bypass surgery several years prior to pregnancy. Temperature is 37 C (98.6 F), pulse is 190/min, and respirations are 60/min. The patient is in moderate respiratory distress and has an enlarged liver. Physical examination is otherwise normal. Chest radiography reveals cardiomegaly. Further work-up shows impaired carbohydrate metabolism with increased serum levels of lactate and decreased erythrocyte transketolase activity. Which of the following additional enzymes is most likely to have impaired activity in this patient?

○ A. Alpha-1,4-glucosidase
○ B. Alpha-L-iduronidase
○ C. Galactose-1-phosphate uridyltransferase
○ D. Glucose-6-phosphatase
○ E. Pyruvate dehydrogenase


Item 21 of 40
Question Id: 107111
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Settings

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● A. Alpha-1,4-glucosidase
○ B. Alpha-L-iduronidase
○ C. Galactose-1-phosphate uridyltransferase
○ D. Glucose-6-phosphatase
○ E. Pyruvate dehydrogenase

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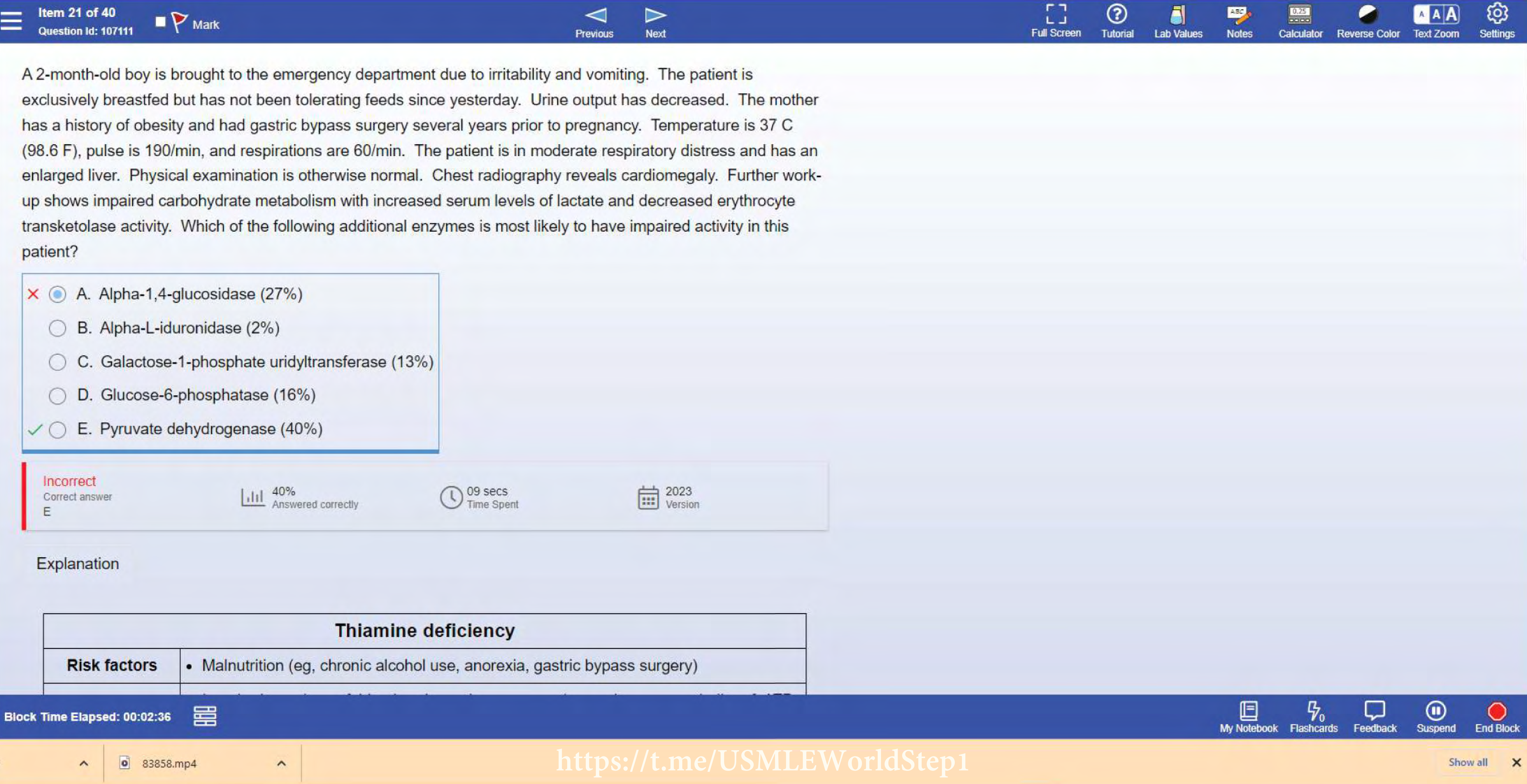
Item 21 of 40
Question Id: 107111
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
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✗ ● A. Alpha-1,4-glucosidase (27%)
○ B. Alpha-L-iduronidase (2%)
○ C. Galactose-1-phosphate uridyltransferase (13%)
○ D. Glucose-6-phosphatase (16%)
✓ ○ E. Pyruvate dehydrogenase (40%)

Incorrect
Correct answer
E

40%
Answered correctly

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Explanation

Thiamine deficiency	
Risk factors	• Malnutrition (eg, chronic alcohol use, anorexia, gastric bypass surgery)

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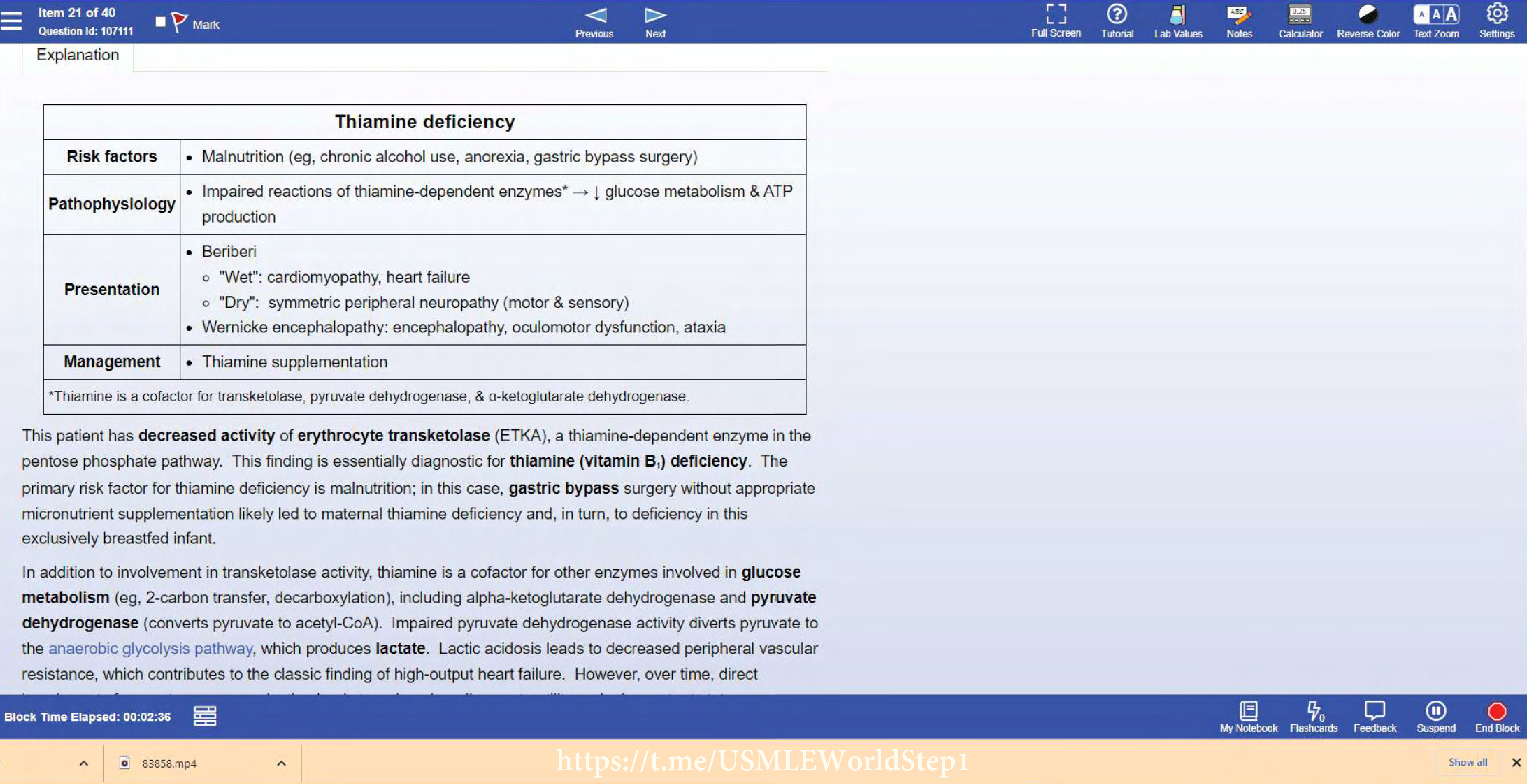
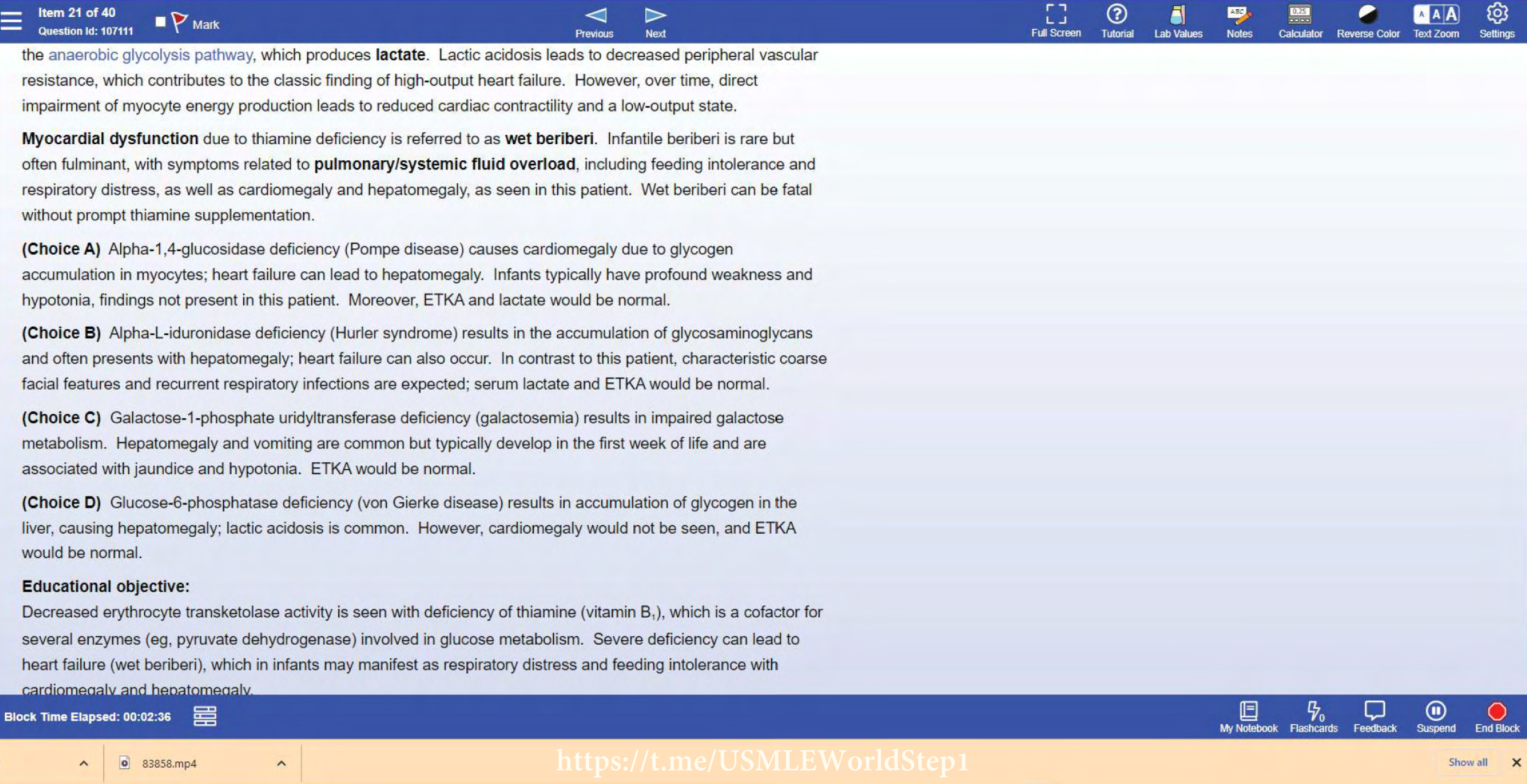

Item 21 of 40
Question Id: 107111
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:02:36
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Thiamine deficiency	
Risk factors	• Malnutrition (eg, chronic alcohol use, anorexia, gastric bypass surgery)
Pathophysiology	• Impaired reactions of thiamine-dependent enzymes* → ↓ glucose metabolism & ATP production
Presentation	• Beriberi ◦ "Wet": cardiomyopathy, heart failure ◦ "Dry": symmetric peripheral neuropathy (motor & sensory) • Wernicke encephalopathy: encephalopathy, oculomotor dysfunction, ataxia
Management	• Thiamine supplementation
*Thiamine is a cofactor for transketolase, pyruvate dehydrogenase, & α-ketoglutarate dehydrogenase.	

This patient has **decreased activity** of **erythrocyte transketolase** (ETKA), a thiamine-dependent enzyme in the pentose phosphate pathway. This finding is essentially diagnostic for **thiamine (vitamin B_1) deficiency**. The primary risk factor for thiamine deficiency is malnutrition; in this case, **gastric bypass** surgery without appropriate micronutrient supplementation likely led to maternal thiamine deficiency and, in turn, to deficiency in this exclusively breastfed infant.

In addition to involvement in transketolase activity, thiamine is a cofactor for other enzymes involved in **glucose metabolism** (eg, 2-carbon transfer, decarboxylation), including alpha-ketoglutarate dehydrogenase and **pyruvate dehydrogenase** (converts pyruvate to acetyl-CoA). Impaired pyruvate dehydrogenase activity diverts pyruvate to the anaerobic glycolysis pathway, which produces **lactate**. Lactic acidosis leads to decreased peripheral vascular resistance, which contributes to the classic finding of high-output heart failure. However, over time, direct



the anaerobic glycolysis pathway, which produces **lactate**. Lactic acidosis leads to decreased peripheral vascular resistance, which contributes to the classic finding of high-output heart failure. However, over time, direct impairment of myocyte energy production leads to reduced cardiac contractility and a low-output state.

Myocardial dysfunction due to thiamine deficiency is referred to as **wet beriberi**. Infantile beriberi is rare but often fulminant, with symptoms related to **pulmonary/systemic fluid overload**, including feeding intolerance and respiratory distress, as well as cardiomegaly and hepatomegaly, as seen in this patient. Wet beriberi can be fatal without prompt thiamine supplementation.

(Choice A) Alpha-1,4-glucosidase deficiency (Pompe disease) causes cardiomegaly due to glycogen accumulation in myocytes; heart failure can lead to hepatomegaly. Infants typically have profound weakness and hypotonia, findings not present in this patient. Moreover, ETKA and lactate would be normal.

(Choice B) Alpha-L-iduronidase deficiency (Hurler syndrome) results in the accumulation of glycosaminoglycans and often presents with hepatomegaly; heart failure can also occur. In contrast to this patient, characteristic coarse facial features and recurrent respiratory infections are expected; serum lactate and ETKA would be normal.

(Choice C) Galactose-1-phosphate uridyltransferase deficiency (galactosemia) results in impaired galactose metabolism. Hepatomegaly and vomiting are common but typically develop in the first week of life and are associated with jaundice and hypotonia. ETKA would be normal.

(Choice D) Glucose-6-phosphatase deficiency (von Gierke disease) results in accumulation of glycogen in the liver, causing hepatomegaly; lactic acidosis is common. However, cardiomegaly would not be seen, and ETKA would be normal.

Educational objective:

Decreased erythrocyte transketolase activity is seen with deficiency of thiamine (vitamin B_1), which is a cofactor for several enzymes (eg, pyruvate dehydrogenase) involved in glucose metabolism. Severe deficiency can lead to heart failure (wet beriberi), which in infants may manifest as respiratory distress and feeding intolerance with cardiomegaly and hepatomegaly.

- "Dry": symmetric peripheral neuropathy (motor & sensory)

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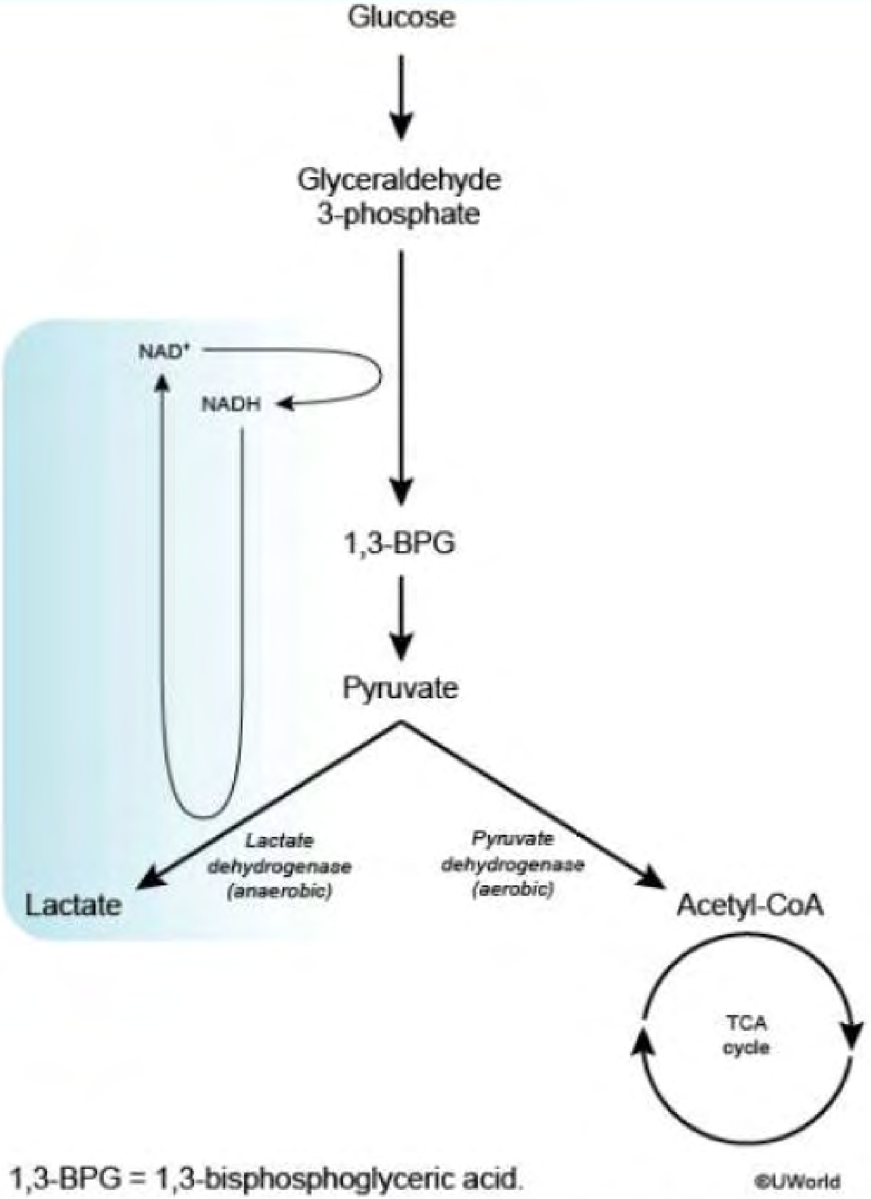
Glucose
Glyceraldehyde 3-phosphate
NAD⁺
NADH
1,3-BPG
Pyruvate
Lactate dehydrogenase (anaerobic)
Pyruvate dehydrogenase (aerobic)
Lactate
Acetyl-CoA
TCA cycle
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1,3-BPG = 1,3-bisphosphoglyceric acid.

(Choice B) Alpha-L-iduronidase deficiency (Hurler syndrome) results in the accumulation of glycosaminoglycans

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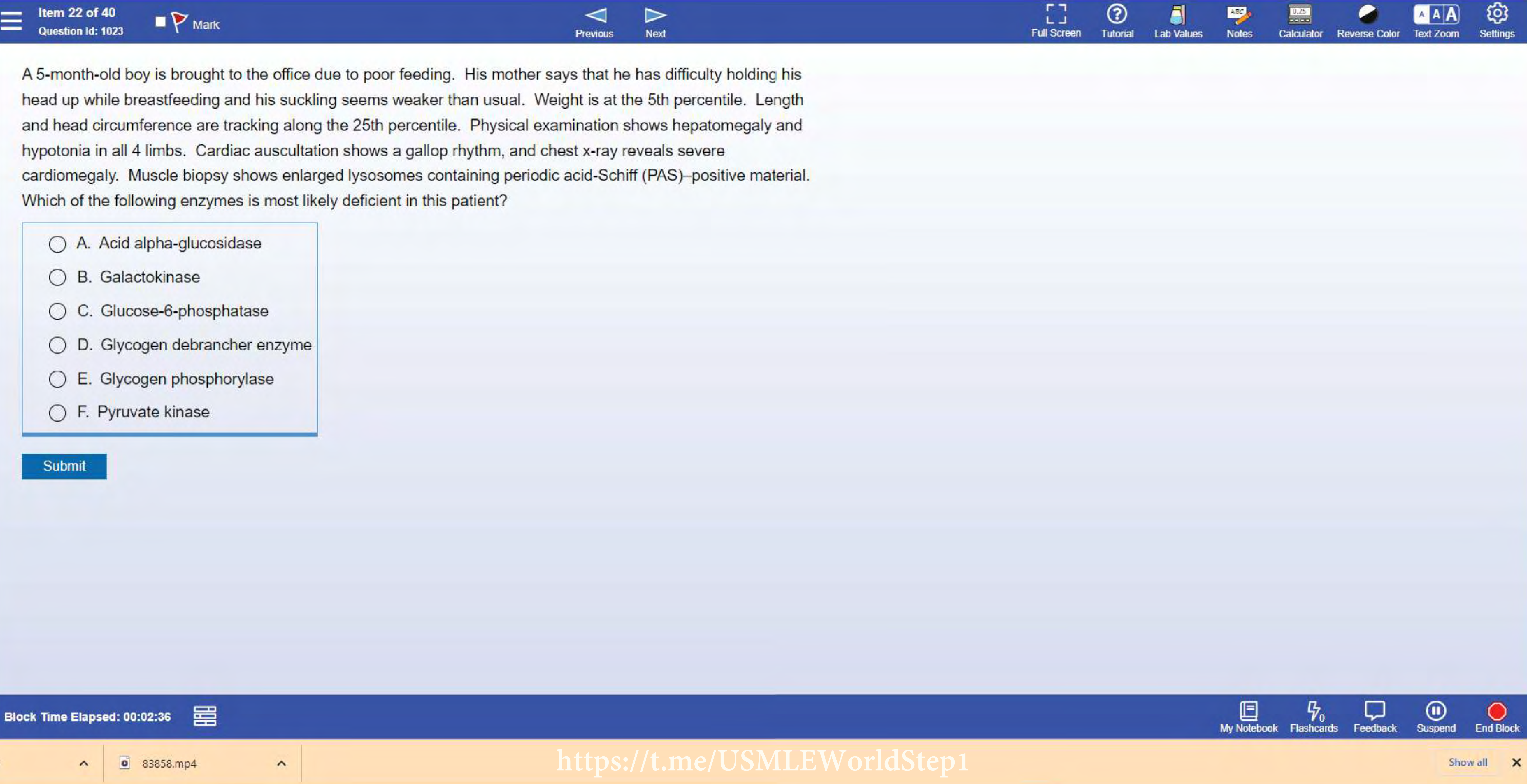
Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 5-month-old boy is brought to the office due to poor feeding. His mother says that he has difficulty holding his head up while breastfeeding and his suckling seems weaker than usual. Weight is at the 5th percentile. Length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation shows a gallop rhythm, and chest x-ray reveals severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)–positive material. Which of the following enzymes is most likely deficient in this patient?

○ A. Acid alpha-glucosidase
○ B. Galactokinase
○ C. Glucose-6-phosphatase
○ D. Glycogen debrancher enzyme
○ E. Glycogen phosphorylase
○ F. Pyruvate kinase

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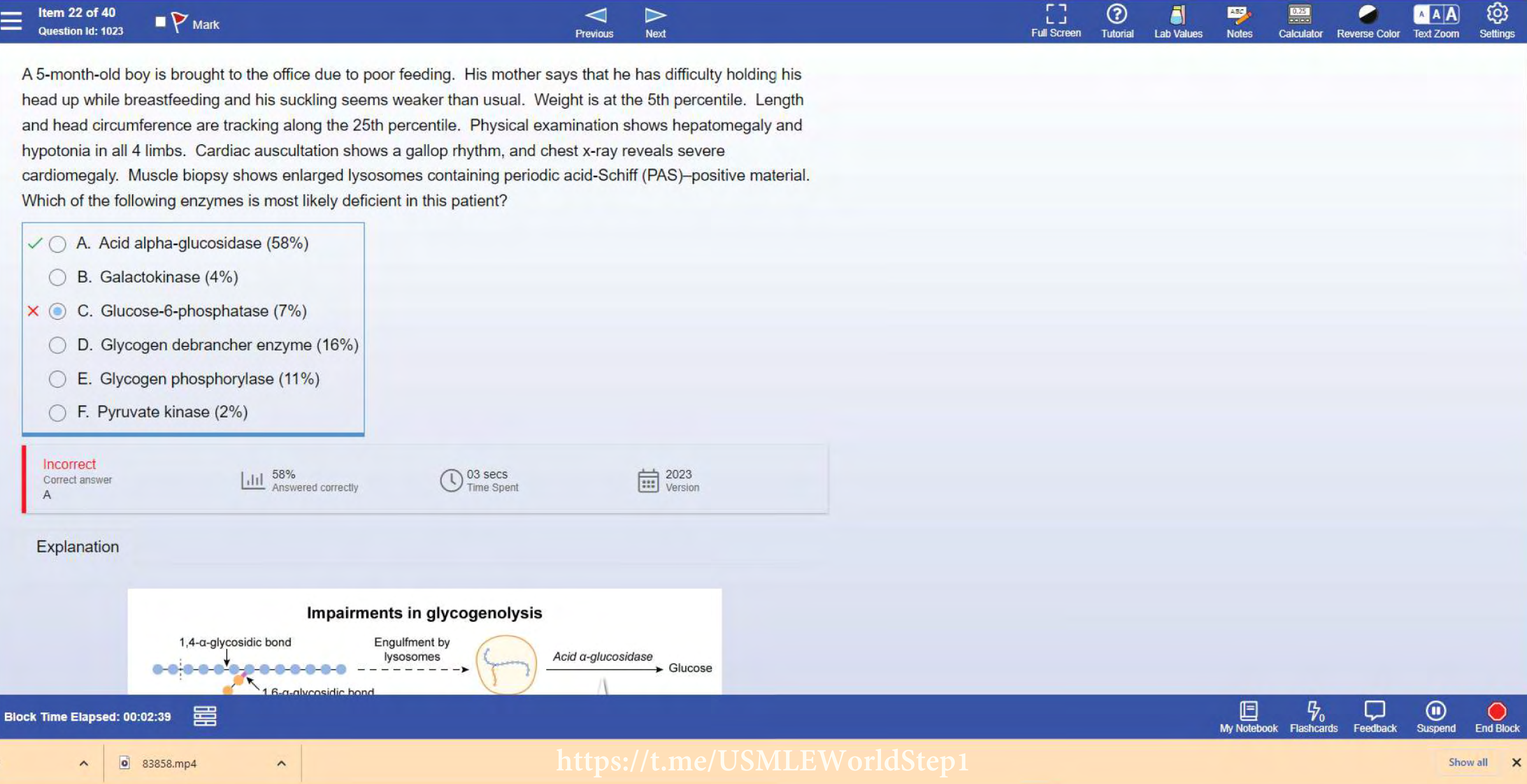
Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✓ ○ A. Acid alpha-glucosidase (58%)
- ○ B. Galactokinase (4%)
- ✗ ● C. Glucose-6-phosphatase (7%)
- ○ D. Glycogen debrancher enzyme (16%)
- ○ E. Glycogen phosphorylase (11%)
- ○ F. Pyruvate kinase (2%)

Incorrect
Correct answer
A

58%
Answered correctly

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2023
Version

Explanation

Impairments in glycogenolysis
1,4-α-glycosidic bond
Engulfment by lysosomes
Acid α-glucosidase
Glucose
1,6-α-glycosidic bond

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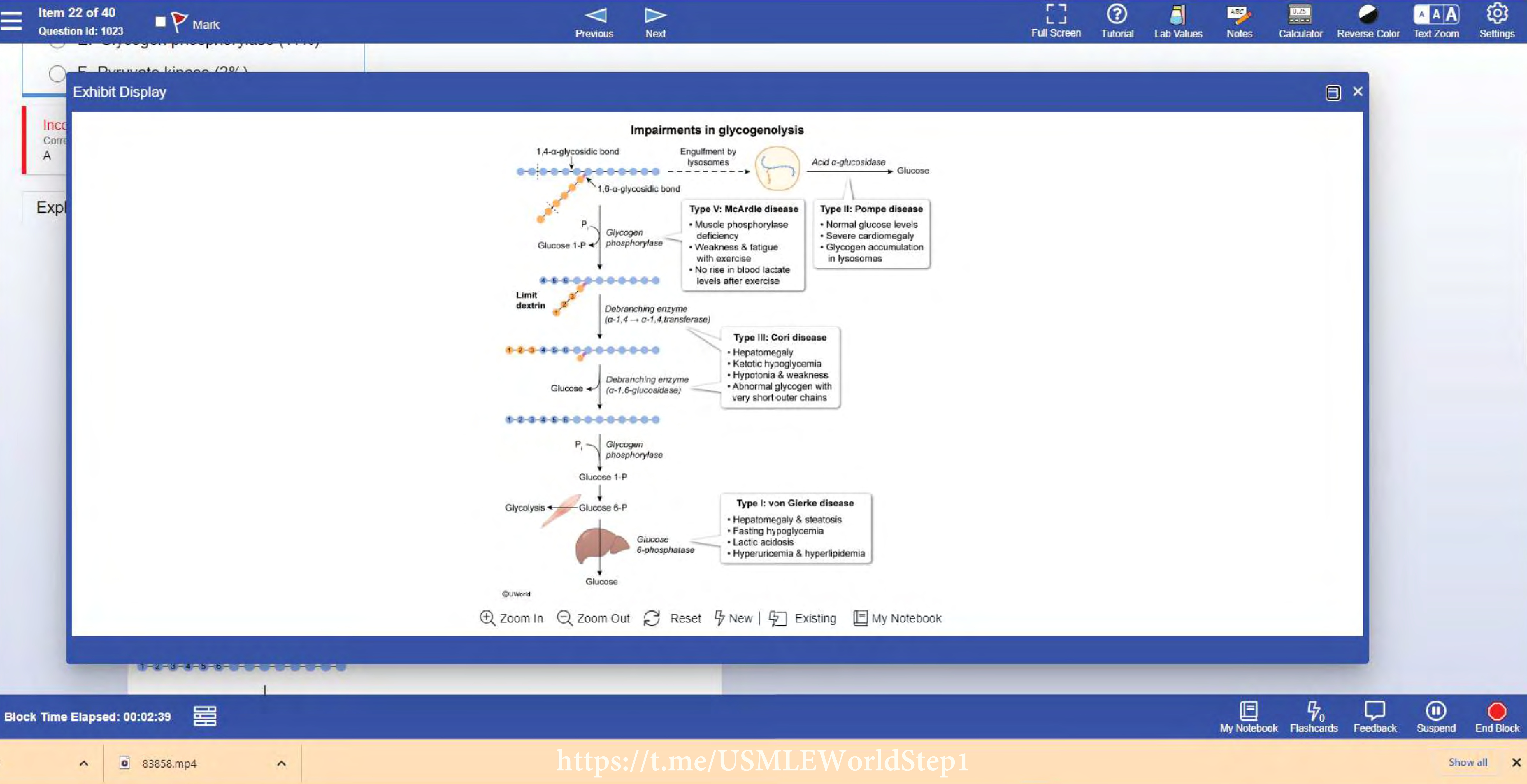
Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
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Settings
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1,4-α-glycosidic bond
Engulfment by lysosomes
Acid α-glucosidase
Glucose
1,6-α-glycosidic bond
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Debranching enzyme (α-1,4 → α-1,4,transferase)
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Glucose
Debranching enzyme (α-1,6-glucosidase)
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P_i
Glycogen phosphorylase
Glucose 1-P
Glycolysis
Glucose 6-P
Glucose 6-phosphatase
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Block Time Elapsed: 00:02:39
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Flashcards
Feedback
Suspend
End Block
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E. Glycogen phosphorylase (11%)

○ F. Pyruvate kinase (2%)

Inco
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Expl

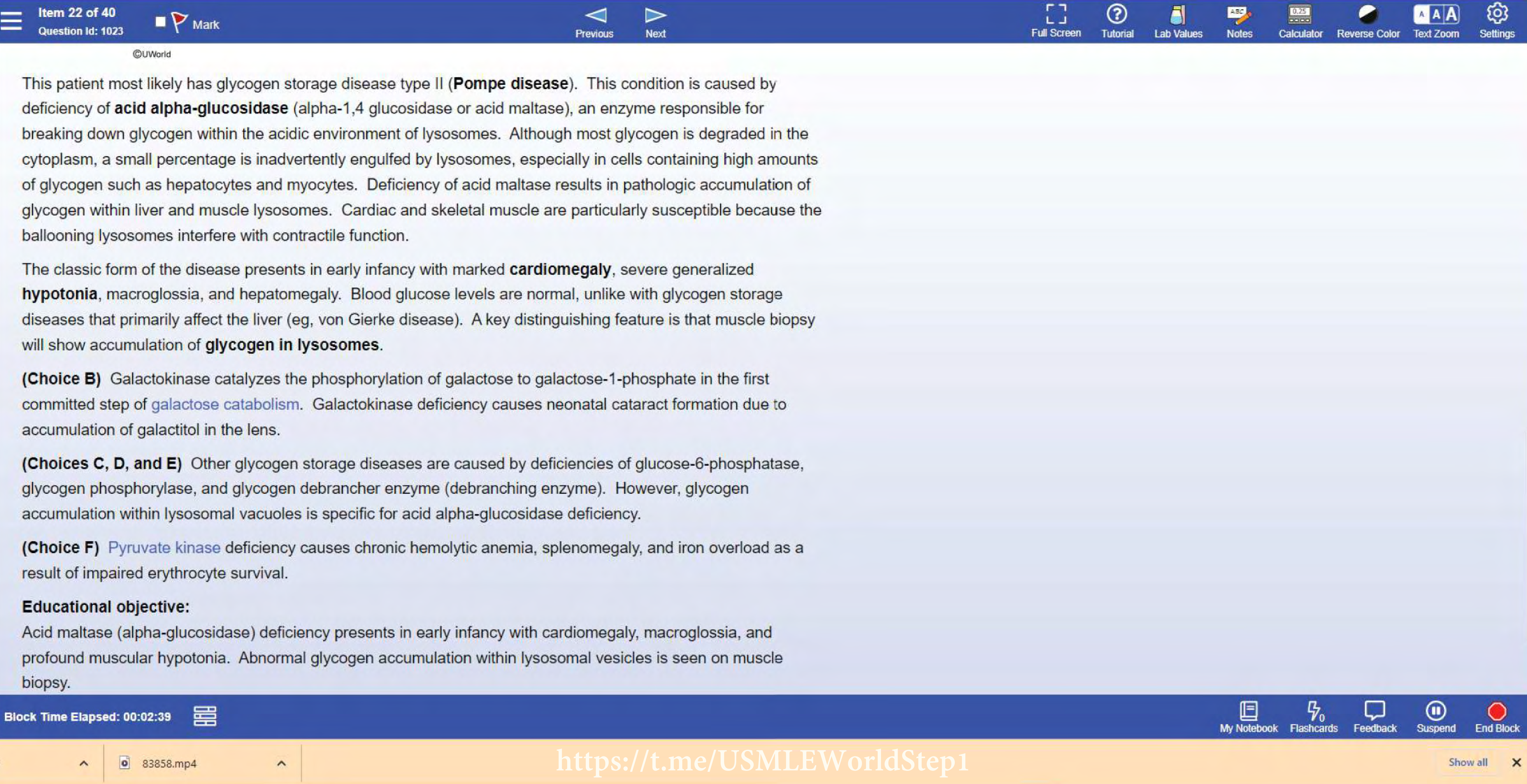
Impairments in glycogenolysis

Type V: McArdle disease
- Muscle phosphorylase deficiency
- Weakness & fatigue with exercise
- No rise in blood lactate levels after exercise

Type II: Pompe disease
- Normal glucose levels
- Severe cardiomegaly
- Glycogen accumulation in lysosomes

Type III: Cori disease
- Hepatomegaly
- Ketotic hypoglycemia
- Hypotonia & weakness
- Abnormal glycogen with very short outer chains

Type I: von Gierke disease
- Hepatomegaly & steatosis
- Fasting hypoglycemia
- Lactic acidosis
- Hyperuricemia & hyperlipidemia


Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid alpha-glucosidase** (alpha-1,4 glucosidase or acid maltase), an enzyme responsible for breaking down glycogen within the acidic environment of lysosomes. Although most glycogen is degraded in the cytoplasm, a small percentage is inadvertently engulfed by lysosomes, especially in cells containing high amounts of glycogen such as hepatocytes and myocytes. Deficiency of acid maltase results in pathologic accumulation of glycogen within liver and muscle lysosomes. Cardiac and skeletal muscle are particularly susceptible because the ballooning lysosomes interfere with contractile function.

The classic form of the disease presents in early infancy with marked **cardiomegaly**, severe generalized **hypotonia**, macroglossia, and hepatomegaly. Blood glucose levels are normal, unlike with glycogen storage diseases that primarily affect the liver (eg, von Gierke disease). A key distinguishing feature is that muscle biopsy will show accumulation of **glycogen in lysosomes**.

(Choice B) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of galactose catabolism. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

(Choices C, D, and E) Other glycogen storage diseases are caused by deficiencies of glucose-6-phosphatase, glycogen phosphorylase, and glycogen debrancher enzyme (debranching enzyme). However, glycogen accumulation within lysosomal vacuoles is specific for acid alpha-glucosidase deficiency.

(Choice F) Pyruvate kinase deficiency causes chronic hemolytic anemia, splenomegaly, and iron overload as a result of impaired erythrocyte survival.

Educational objective:
Acid maltase (alpha-glucosidase) deficiency presents in early infancy with cardiomegaly, macroglossia, and profound muscular hypotonia. Abnormal glycogen accumulation within lysosomal vesicles is seen on muscle biopsy.

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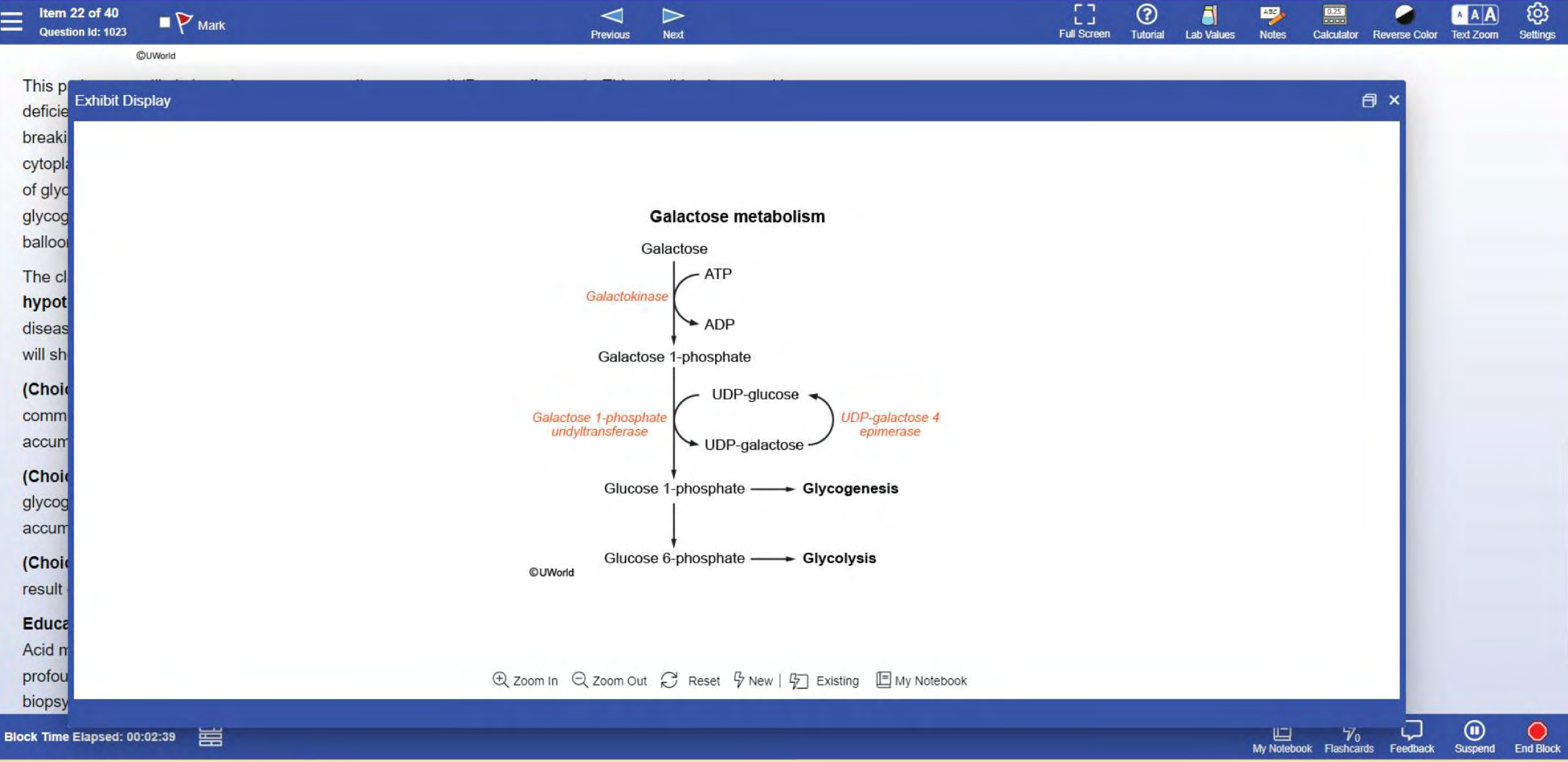
Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Galactose metabolism
Galactose
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Galactokinase
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Galactose 1-phosphate
UDP-glucose
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UDP-galactose 4 epimerase
UDP-galactose
Glucose 1-phosphate
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Glucose 6-phosphate
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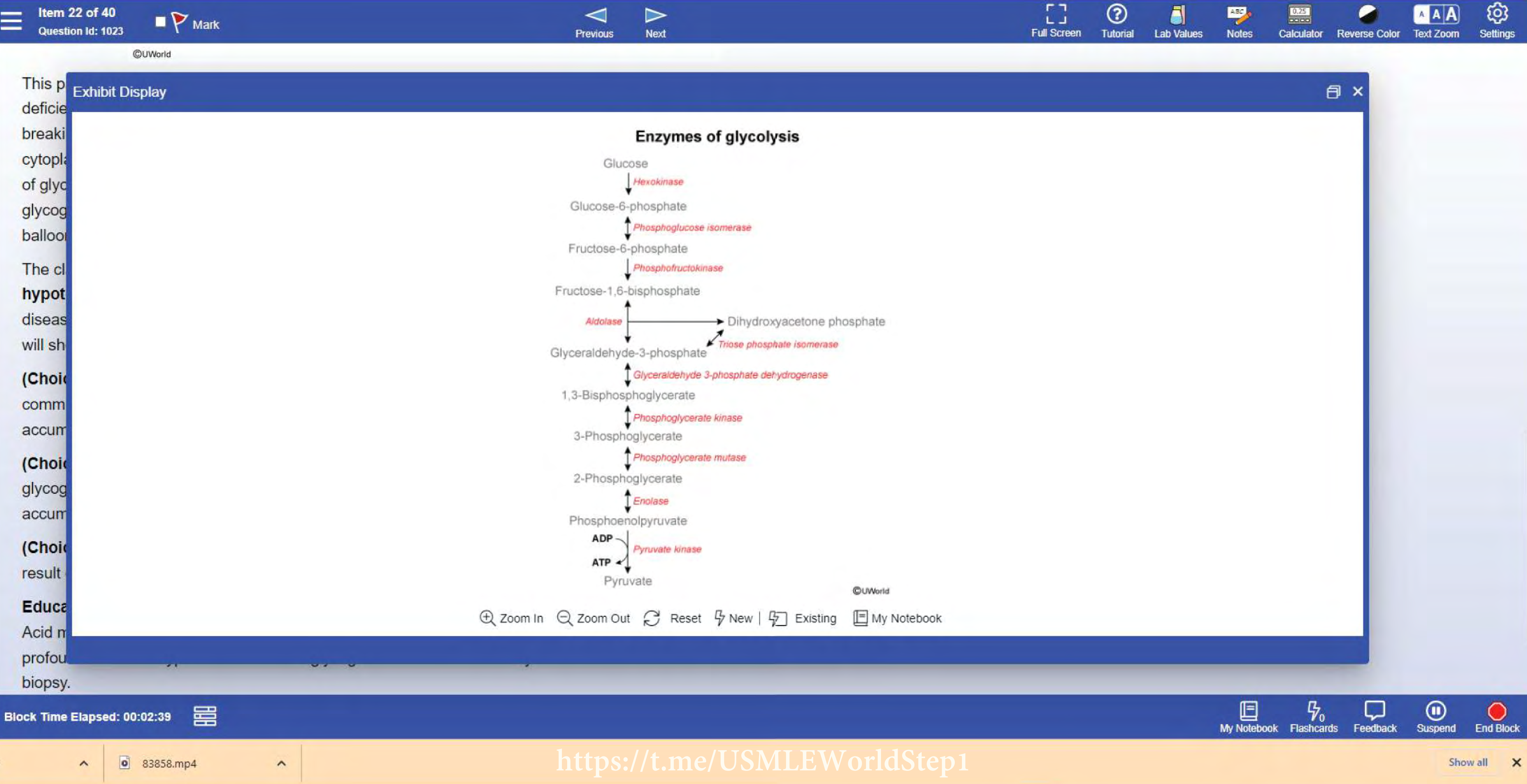
Item 22 of 40
Question Id: 1023
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Enzymes of glycolysis

Glucose
Hexokinase
Glucose-6-phosphate
Phosphoglucose isomerase
Fructose-6-phosphate
Phosphofructokinase
Fructose-1,6-bisphosphate
Aldolase
Dihydroxyacetone phosphate
Triose phosphate isomerase
Glyceraldehyde-3-phosphate
Glyceraldehyde 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
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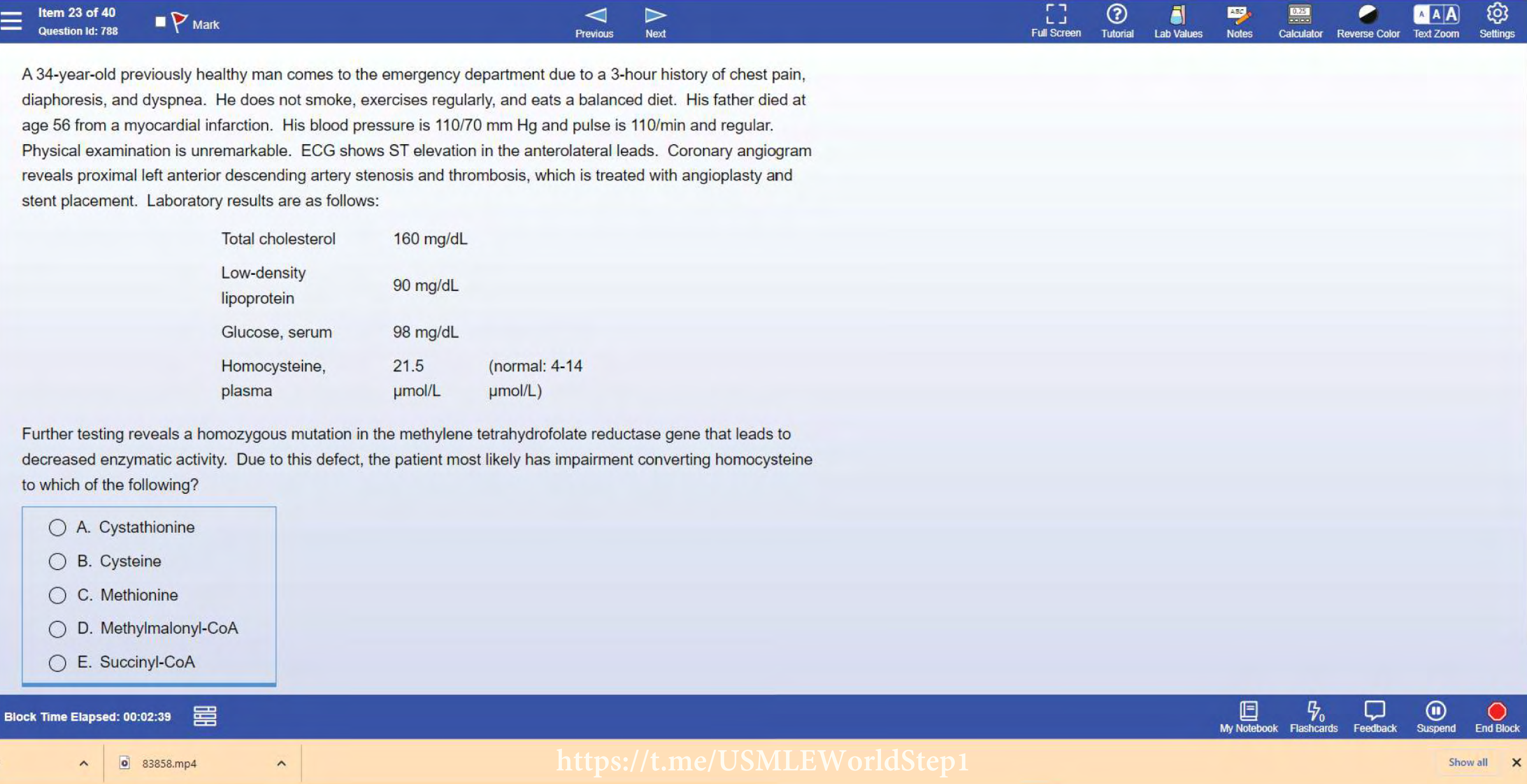
Item 23 of 40
Question Id: 788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 34-year-old previously healthy man comes to the emergency department due to a 3-hour history of chest pain, diaphoresis, and dyspnea. He does not smoke, exercises regularly, and eats a balanced diet. His father died at age 56 from a myocardial infarction. His blood pressure is 110/70 mm Hg and pulse is 110/min and regular. Physical examination is unremarkable. ECG shows ST elevation in the anterolateral leads. Coronary angiogram reveals proximal left anterior descending artery stenosis and thrombosis, which is treated with angioplasty and stent placement. Laboratory results are as follows:

Total cholesterol	160 mg/dL	
Low-density lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

○ A. Cystathionine
○ B. Cysteine
○ C. Methionine
○ D. Methylmalonyl-CoA
○ E. Succinyl-CoA

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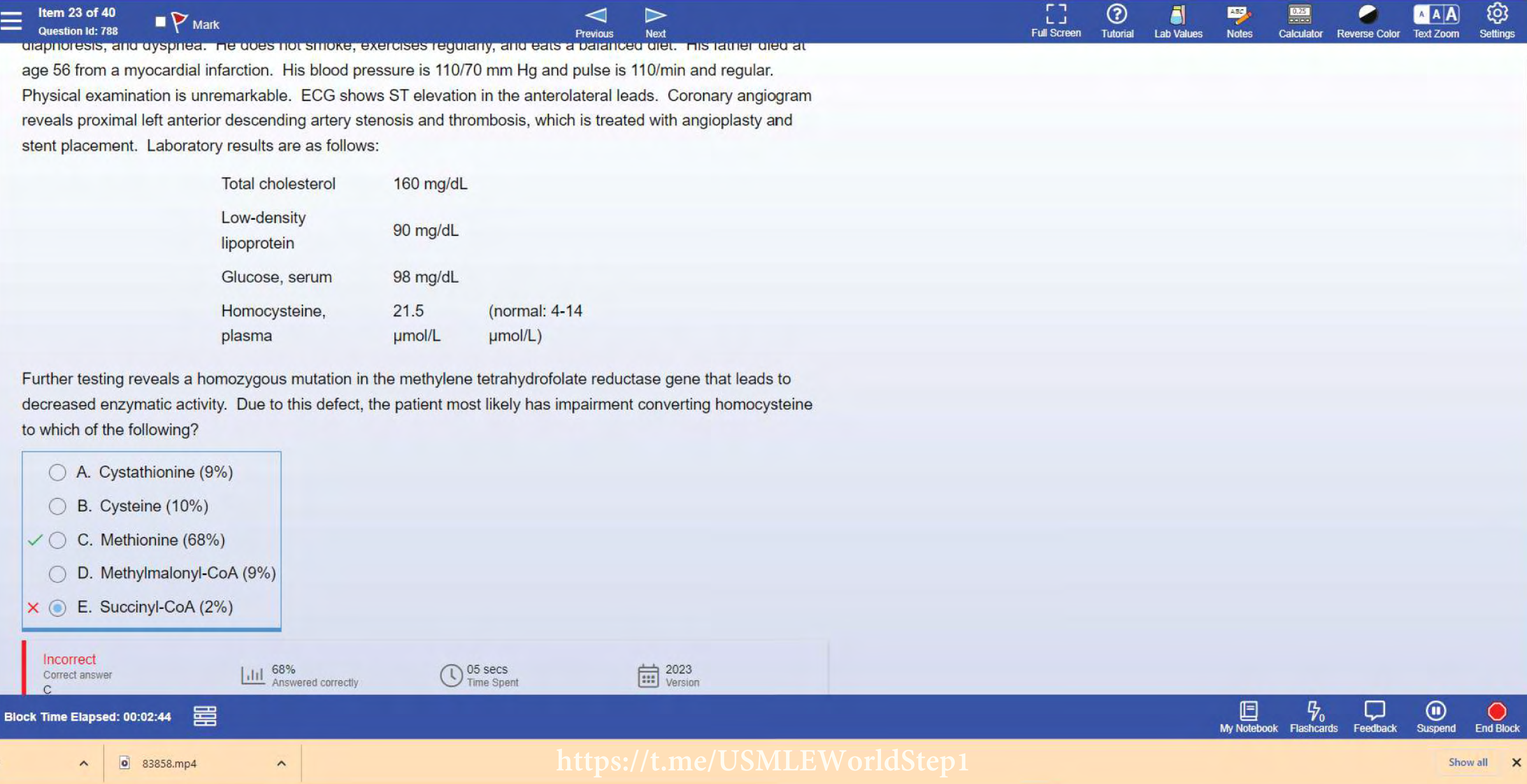
Item 23 of 40
Question Id: 788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

○ A. Cystathionine (9%)
○ B. Cysteine (10%)
✓ ○ C. Methionine (68%)
○ D. Methylmalonyl-CoA (9%)
✗ ● E. Succinyl-CoA (2%)

Incorrect
Correct answer
C

68%
Answered correctly

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Feedback
Suspend
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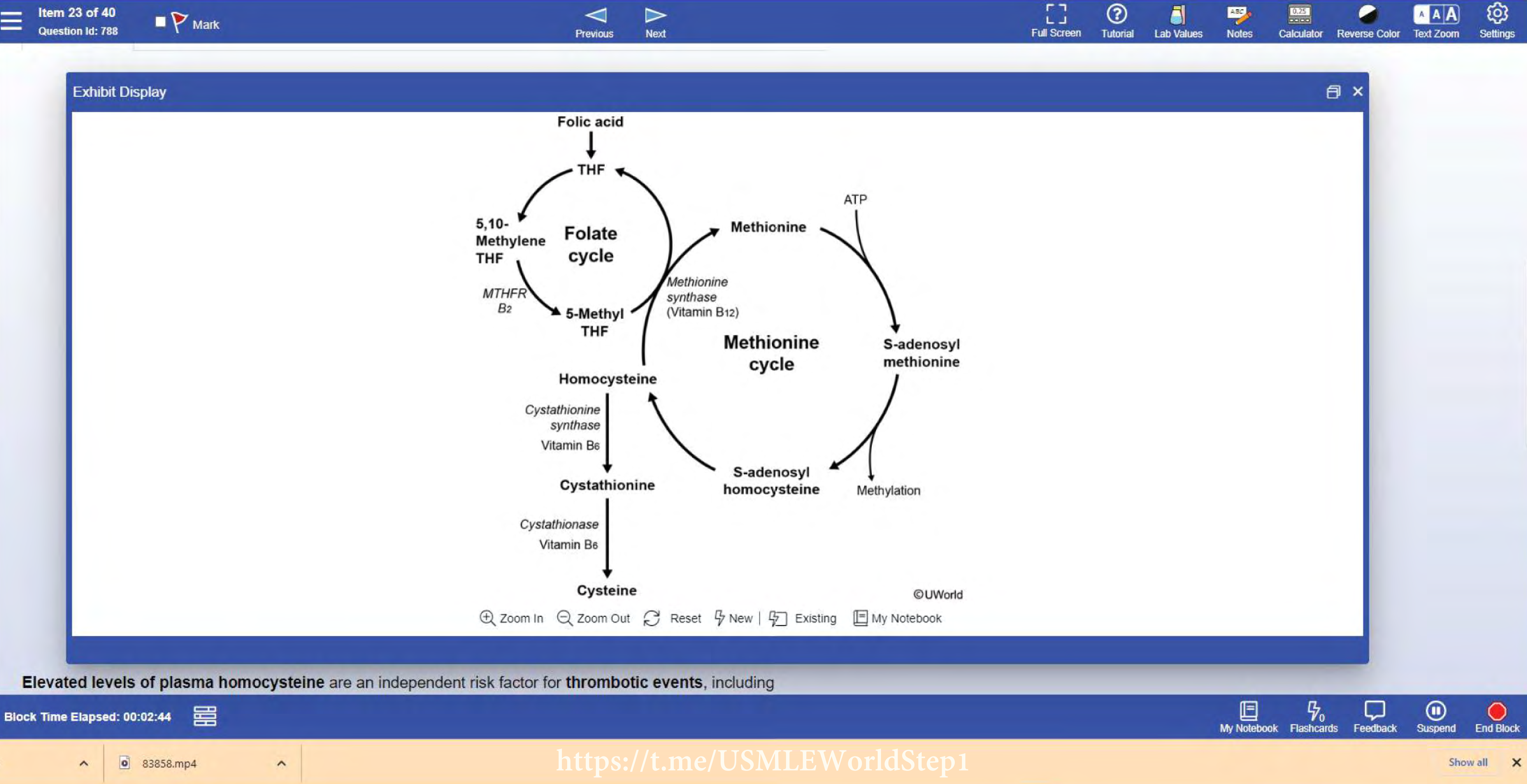
Item 23 of 40
Question Id: 788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Folic acid
THF
5,10-Methylene THF
Folate cycle
MTHFR
B2
5-Methyl THF
Methionine synthase
(Vitamin B12)
Methionine
ATP
S-adenosyl methionine
Methionine cycle
Methylation
S-adenosyl homocysteine
Homocysteine
Cystathionine synthase
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Block Time Elapsed: 00:02:44
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Suspend
End Block
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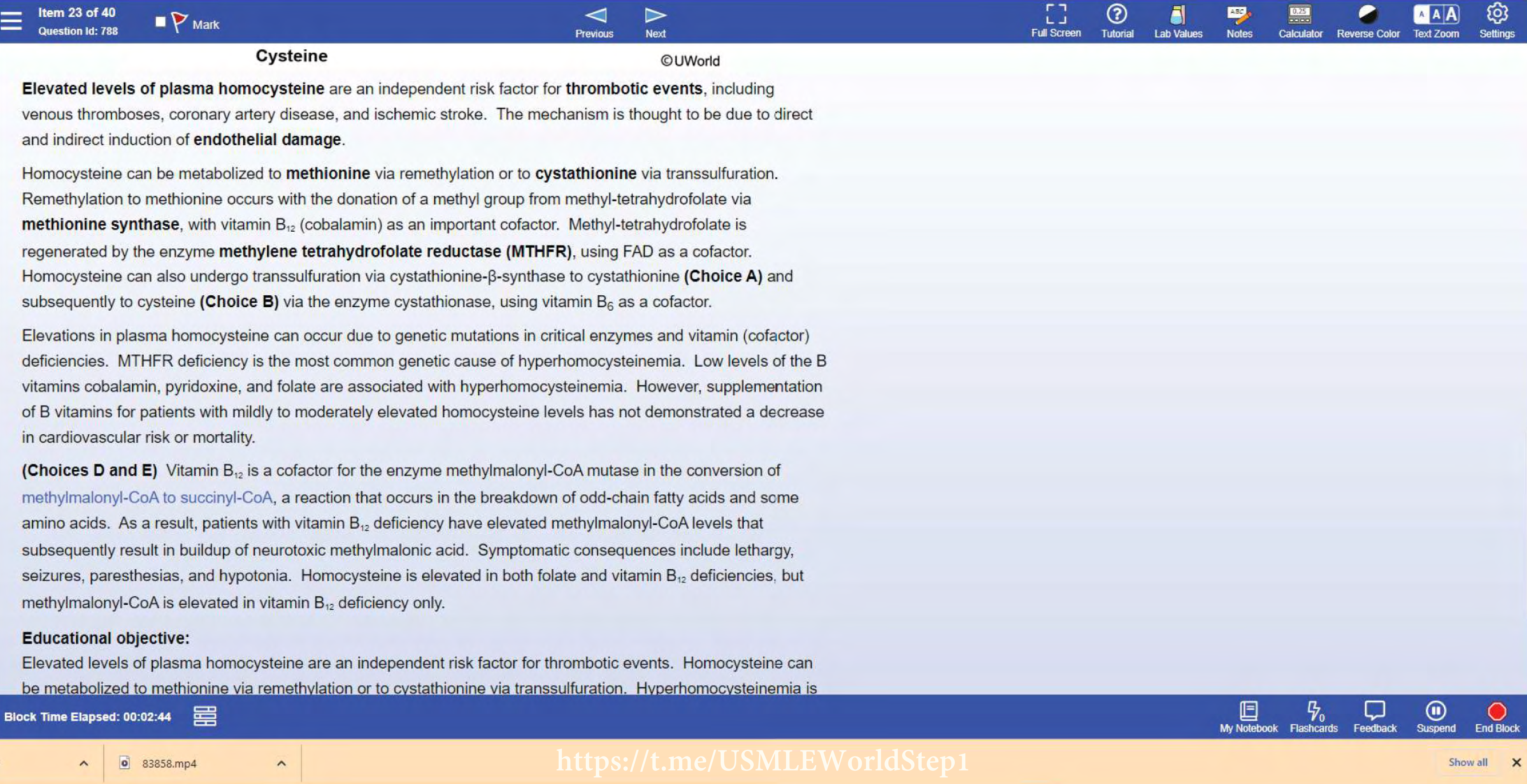
Show all

Elevated levels of plasma homocysteine are an independent risk factor for **thrombotic events**, including



Cysteine

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Elevated levels of plasma homocysteine are an independent risk factor for **thrombotic events**, including venous thromboses, coronary artery disease, and ischemic stroke. The mechanism is thought to be due to direct and indirect induction of **endothelial damage**.

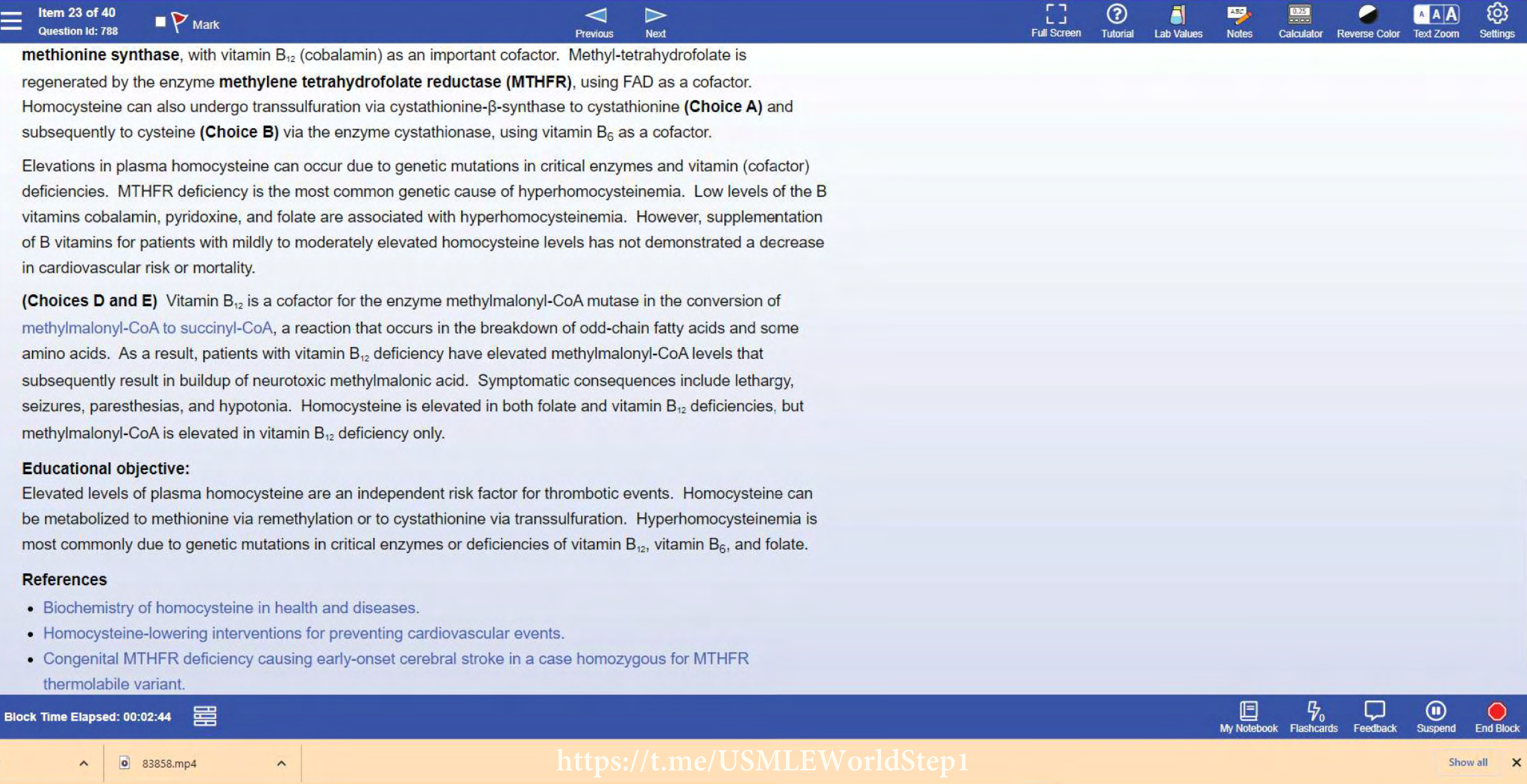
Homocysteine can be metabolized to **methionine** via remethylation or to **cystathionine** via transsulfuration. Remethylation to methionine occurs with the donation of a methyl group from methyl-tetrahydrofolate via **methionine synthase**, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is regenerated by the enzyme **methylene tetrahydrofolate reductase (MTHFR)**, using FAD as a cofactor. Homocysteine can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the enzyme cystathionase, using vitamin B_6 as a cofactor.

Elevations in plasma homocysteine can occur due to genetic mutations in critical enzymes and vitamin (cofactor) deficiencies. MTHFR deficiency is the most common genetic cause of hyperhomocysteinemia. Low levels of the B vitamins cobalamin, pyridoxine, and folate are associated with hyperhomocysteinemia. However, supplementation of B vitamins for patients with mildly to moderately elevated homocysteine levels has not demonstrated a decrease in cardiovascular risk or mortality.

(Choices D and E) Vitamin B_{12} is a cofactor for the enzyme methylmalonyl-CoA mutase in the conversion of methylmalonyl-CoA to succinyl-CoA, a reaction that occurs in the breakdown of odd-chain fatty acids and some amino acids. As a result, patients with vitamin B_{12} deficiency have elevated methylmalonyl-CoA levels that subsequently result in buildup of neurotoxic methylmalonic acid. Symptomatic consequences include lethargy, seizures, paresthesias, and hypotonia. Homocysteine is elevated in both folate and vitamin B_{12} deficiencies, but methylmalonyl-CoA is elevated in vitamin B_{12} deficiency only.

Educational objective:

Elevated levels of plasma homocysteine are an independent risk factor for thrombotic events. Homocysteine can be metabolized to methionine via remethylation or to cystathionine via transsulfuration. Hyperhomocysteinemia is



methionine synthase, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is regenerated by the enzyme **methylene tetrahydrofolate reductase (MTHFR)**, using FAD as a cofactor. Homocysteine can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the enzyme cystathionase, using vitamin B_6 as a cofactor.

Elevations in plasma homocysteine can occur due to genetic mutations in critical enzymes and vitamin (cofactor) deficiencies. MTHFR deficiency is the most common genetic cause of hyperhomocysteinemia. Low levels of the B vitamins cobalamin, pyridoxine, and folate are associated with hyperhomocysteinemia. However, supplementation of B vitamins for patients with mildly to moderately elevated homocysteine levels has not demonstrated a decrease in cardiovascular risk or mortality.

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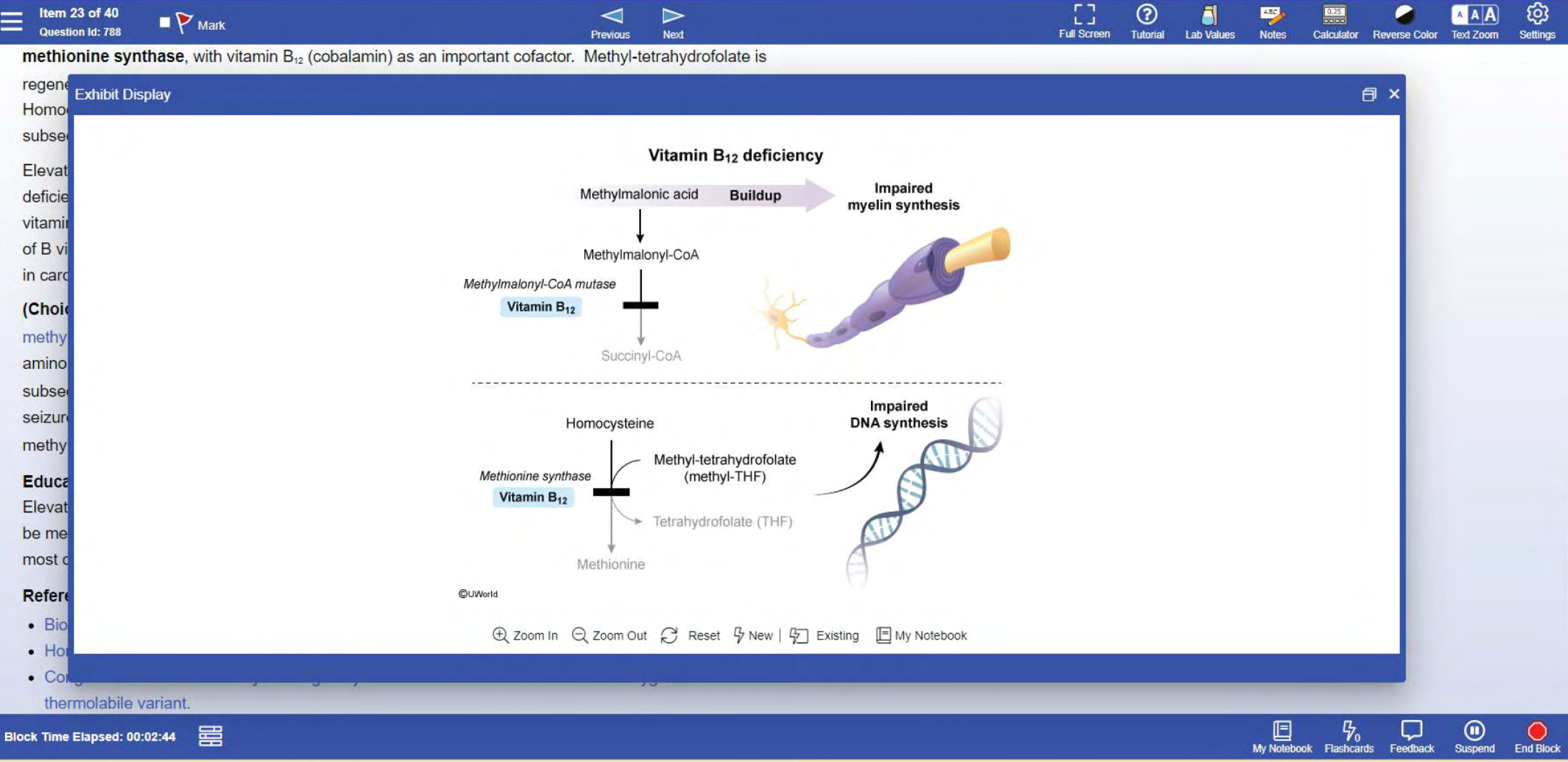
Educational objective:

Elevated levels of plasma homocysteine are an independent risk factor for thrombotic events. Homocysteine can be metabolized to methionine via remethylation or to cystathionine via transsulfuration. Hyperhomocysteinemia is most commonly due to genetic mutations in critical enzymes or deficiencies of vitamin B_{12}, vitamin B_6, and folate.

References

- Biochemistry of homocysteine in health and diseases.
- Homocysteine-lowering interventions for preventing cardiovascular events.
- Congenital MTHFR deficiency causing early-onset cerebral stroke in a case homozygous for MTHFR thermolabile variant.


Item 23 of 40
Question Id: 788
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Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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methionine synthase, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is

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Exhibit Display

Vitamin B_{12} deficiency

Methylmalonic acid
Buildup
Impaired myelin synthesis
Methylmalonyl-CoA
Methylmalonyl-CoA mutase
Vitamin B12
Succinyl-CoA
Homocysteine
Impaired DNA synthesis
Methyl-tetrahydrofolate (methyl-THF)
Methionine synthase
Vitamin B12
Tetrahydrofolate (THF)
Methionine
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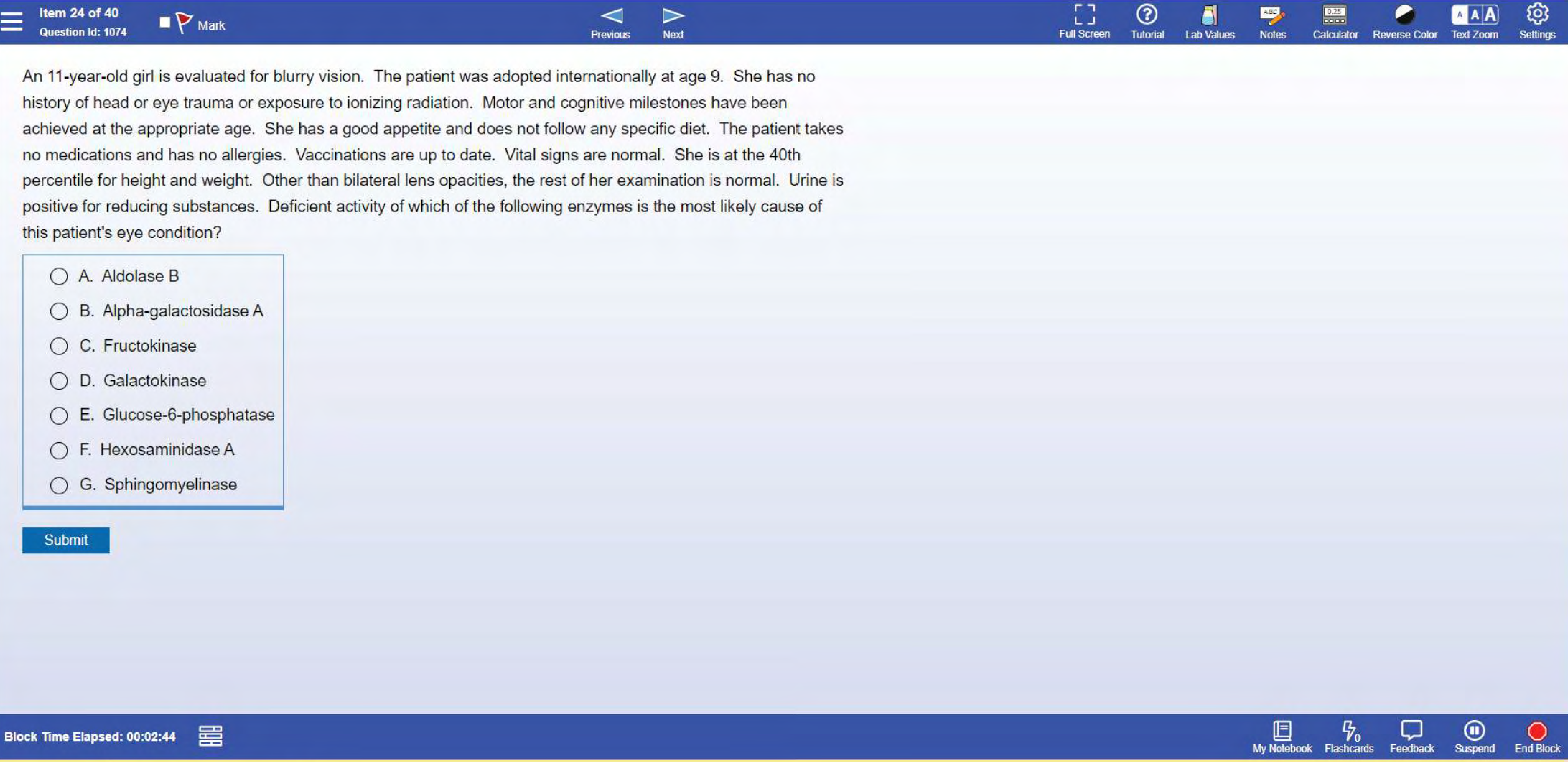
Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 11-year-old girl is evaluated for blurry vision. The patient was adopted internationally at age 9. She has no history of head or eye trauma or exposure to ionizing radiation. Motor and cognitive milestones have been achieved at the appropriate age. She has a good appetite and does not follow any specific diet. The patient takes no medications and has no allergies. Vaccinations are up to date. Vital signs are normal. She is at the 40th percentile for height and weight. Other than bilateral lens opacities, the rest of her examination is normal. Urine is positive for reducing substances. Deficient activity of which of the following enzymes is the most likely cause of this patient's eye condition?

○ A. Aldolase B
○ B. Alpha-galactosidase A
○ C. Fructokinase
○ D. Galactokinase
○ E. Glucose-6-phosphatase
○ F. Hexosaminidase A
○ G. Sphingomyelinase

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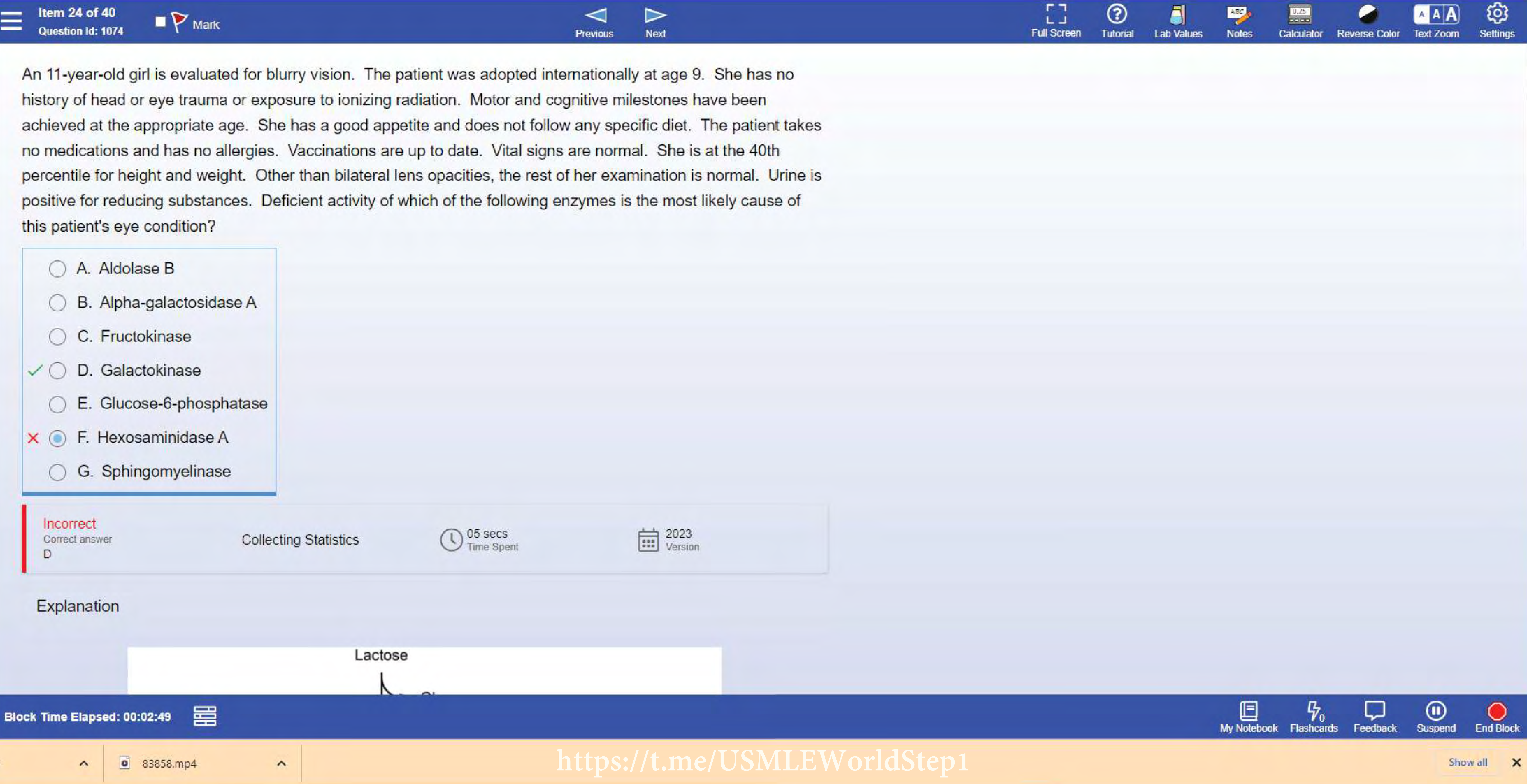
Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ A. Aldolase B
- ○ B. Alpha-galactosidase A
- ○ C. Fructokinase
- ✓ ○ D. Galactokinase
- ○ E. Glucose-6-phosphatase
- ✗ ● F. Hexosaminidase A
- ○ G. Sphingomyelinase

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Correct answer
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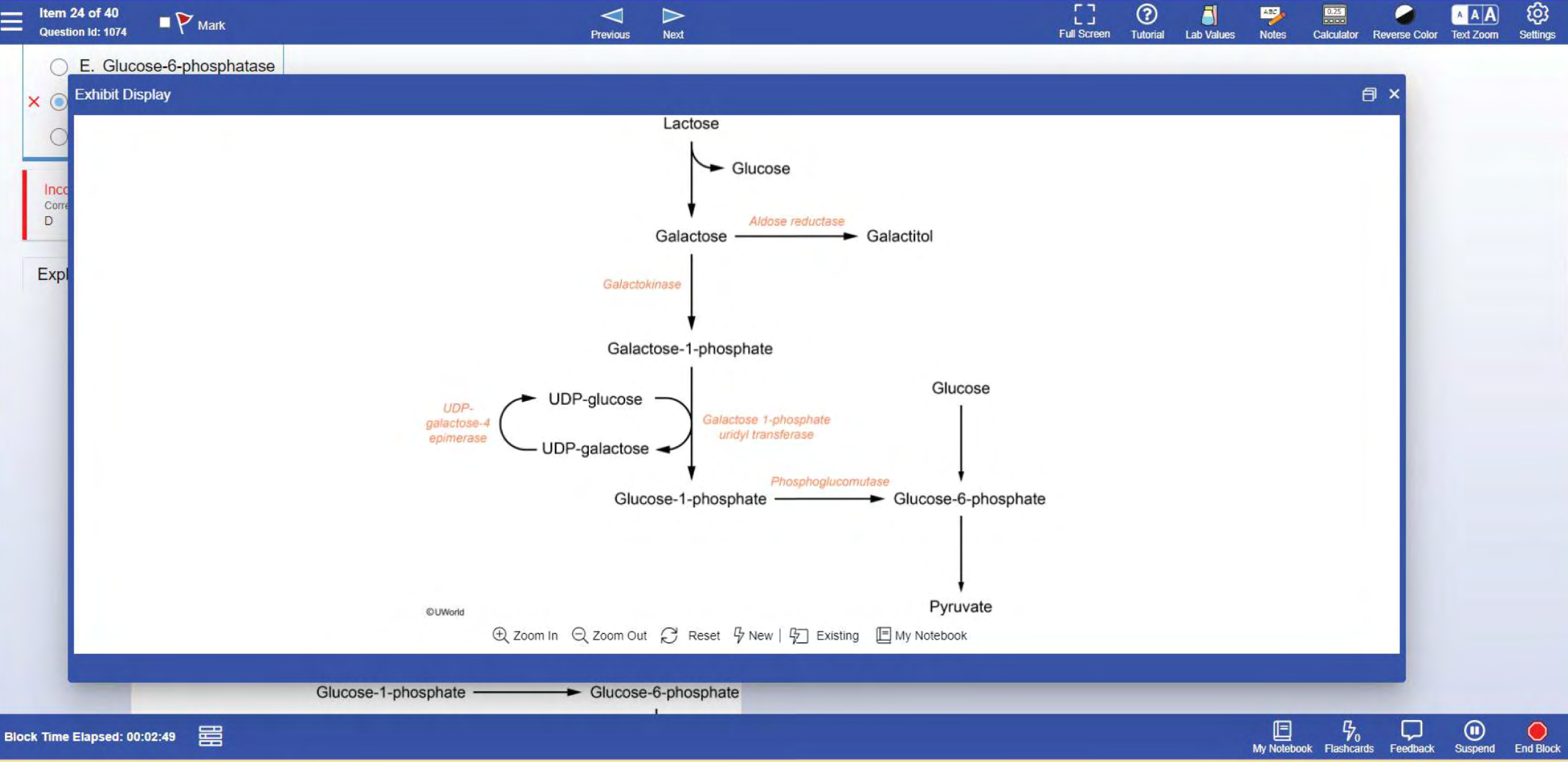
Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
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Aldose reductase
Galactitol
Galactokinase
Galactose-1-phosphate
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○ E. Glucose-6-phosphatase

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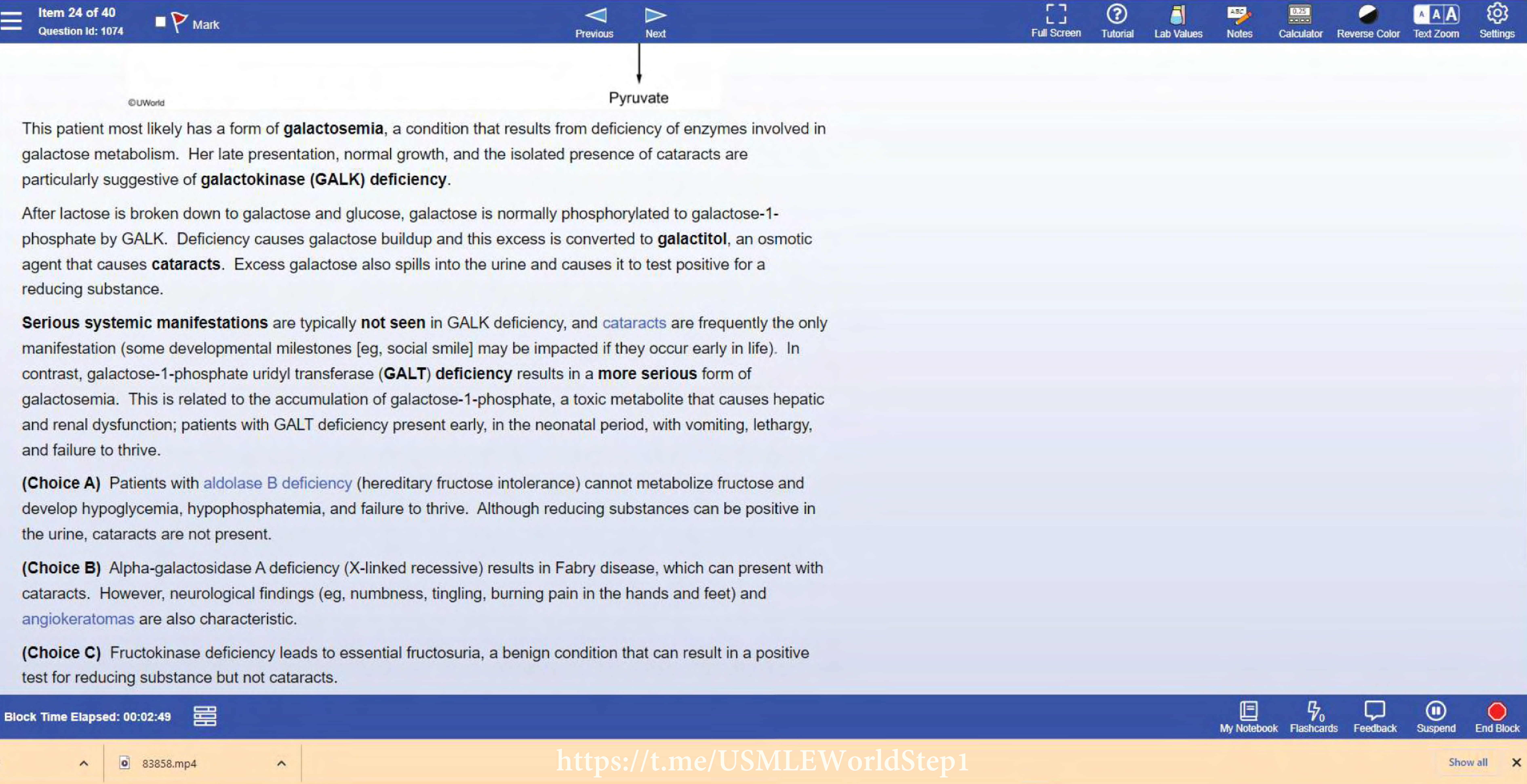
Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Block Time Elapsed: 00:02:49
My Notebook
Flashcards
Feedback
Suspend
End Block
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This patient most likely has a form of **galactosemia**, a condition that results from deficiency of enzymes involved in galactose metabolism. Her late presentation, normal growth, and the isolated presence of cataracts are particularly suggestive of **galactokinase (GALK) deficiency**.

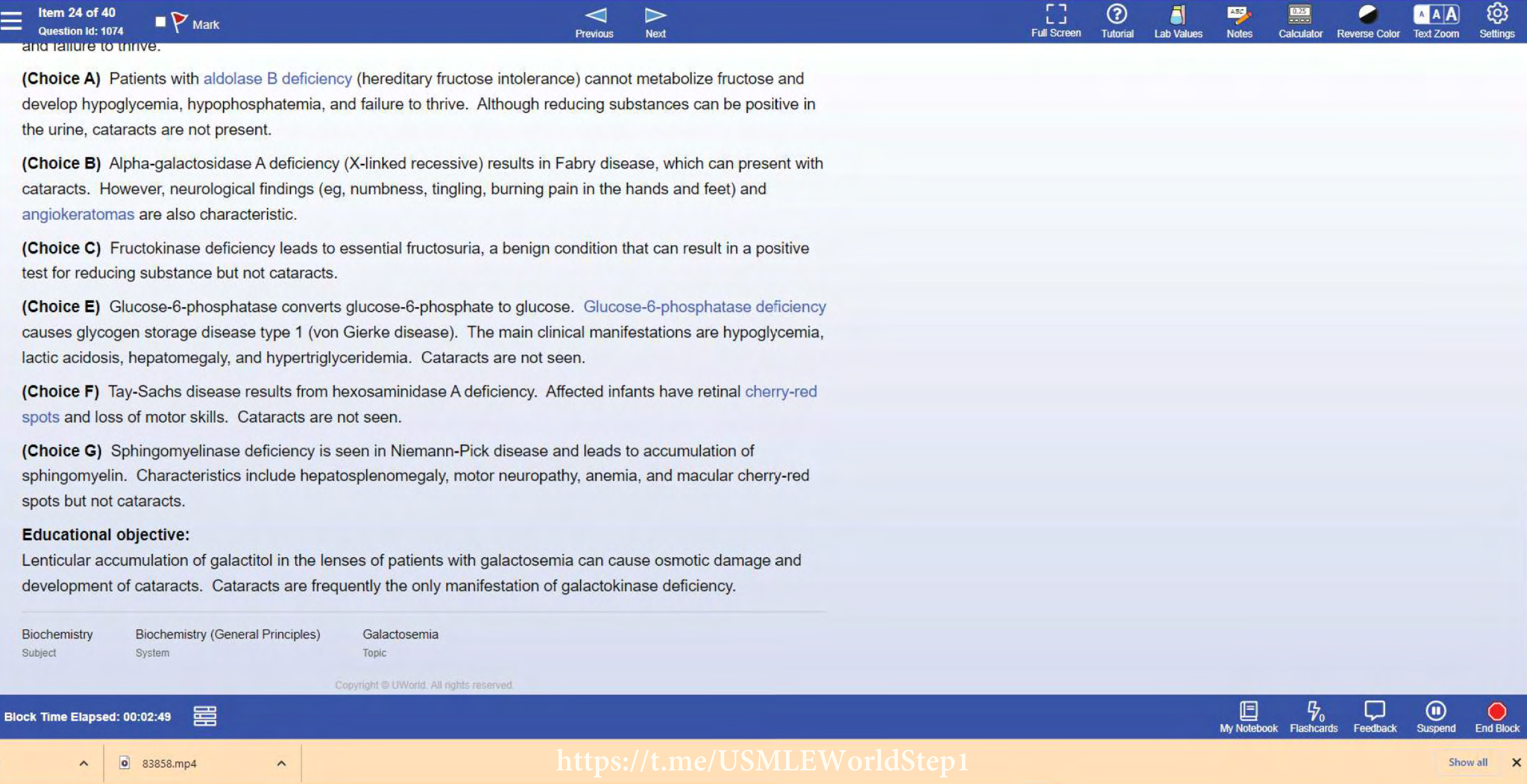
After lactose is broken down to galactose and glucose, galactose is normally phosphorylated to galactose-1-phosphate by GALK. Deficiency causes galactose buildup and this excess is converted to **galactitol**, an osmotic agent that causes **cataracts**. Excess galactose also spills into the urine and causes it to test positive for a reducing substance.

Serious systemic manifestations are typically **not seen** in GALK deficiency, and cataracts are frequently the only manifestation (some developmental milestones [eg, social smile] may be impacted if they occur early in life). In contrast, galactose-1-phosphate uridyl transferase (**GALT**) **deficiency** results in a **more serious** form of galactosemia. This is related to the accumulation of galactose-1-phosphate, a toxic metabolite that causes hepatic and renal dysfunction; patients with GALT deficiency present early, in the neonatal period, with vomiting, lethargy, and failure to thrive.

(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia, hypophosphatemia, and failure to thrive. Although reducing substances can be positive in the urine, cataracts are not present.

(Choice B) Alpha-galactosidase A deficiency (X-linked recessive) results in Fabry disease, which can present with cataracts. However, neurological findings (eg, numbness, tingling, burning pain in the hands and feet) and angiokeratomas are also characteristic.

(Choice C) Fructokinase deficiency leads to essential fructosuria, a benign condition that can result in a positive test for reducing substance but not cataracts.


Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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and failure to thrive.

(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia, hypophosphatemia, and failure to thrive. Although reducing substances can be positive in the urine, cataracts are not present.

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(Choice C) Fructokinase deficiency leads to essential fructosuria, a benign condition that can result in a positive test for reducing substance but not cataracts.

(Choice E) Glucose-6-phosphatase converts glucose-6-phosphate to glucose. Glucose-6-phosphatase deficiency causes glycogen storage disease type 1 (von Gierke disease). The main clinical manifestations are hypoglycemia, lactic acidosis, hepatomegaly, and hypertriglyceridemia. Cataracts are not seen.

(Choice F) Tay-Sachs disease results from hexosaminidase A deficiency. Affected infants have retinal cherry-red spots and loss of motor skills. Cataracts are not seen.

(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

Educational objective:

Lenticular accumulation of galactitol in the lenses of patients with galactosemia can cause osmotic damage and development of cataracts. Cataracts are frequently the only manifestation of galactokinase deficiency.

Biochemistry	Biochemistry (General Principles)	Galactosemia
Subject	System	Topic

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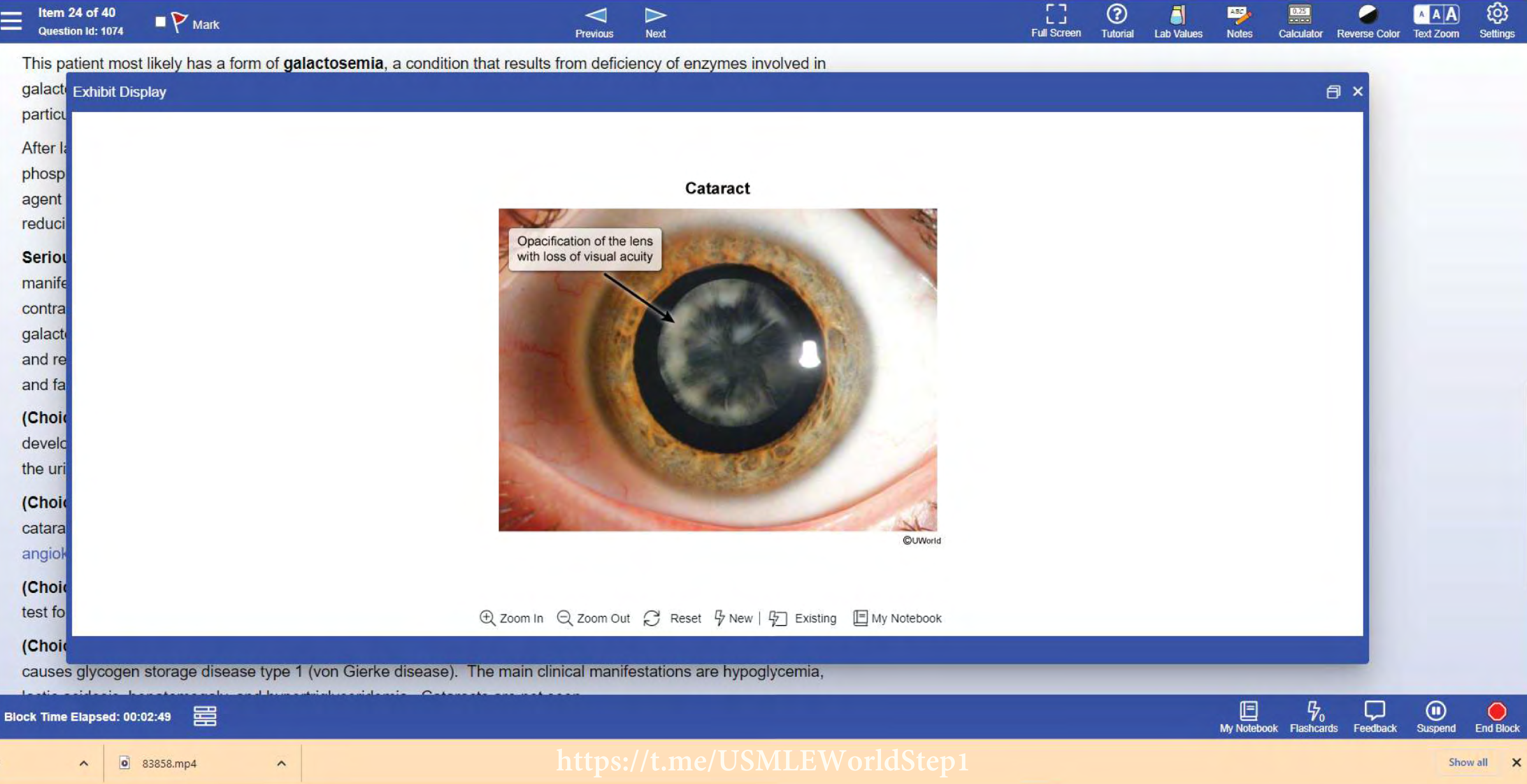
Item 24 of 40
Question Id: 1074
Mark
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Next
Full Screen
Tutorial
Lab Values
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causes glycogen storage disease type 1 (von Gierke disease). The main clinical manifestations are hypoglycemia,
lactic acidosis, hepatomegaly, and hypertriglyceridemia. Cataracts are not seen.

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Cataract

Opacification of the lens with loss of visual acuity
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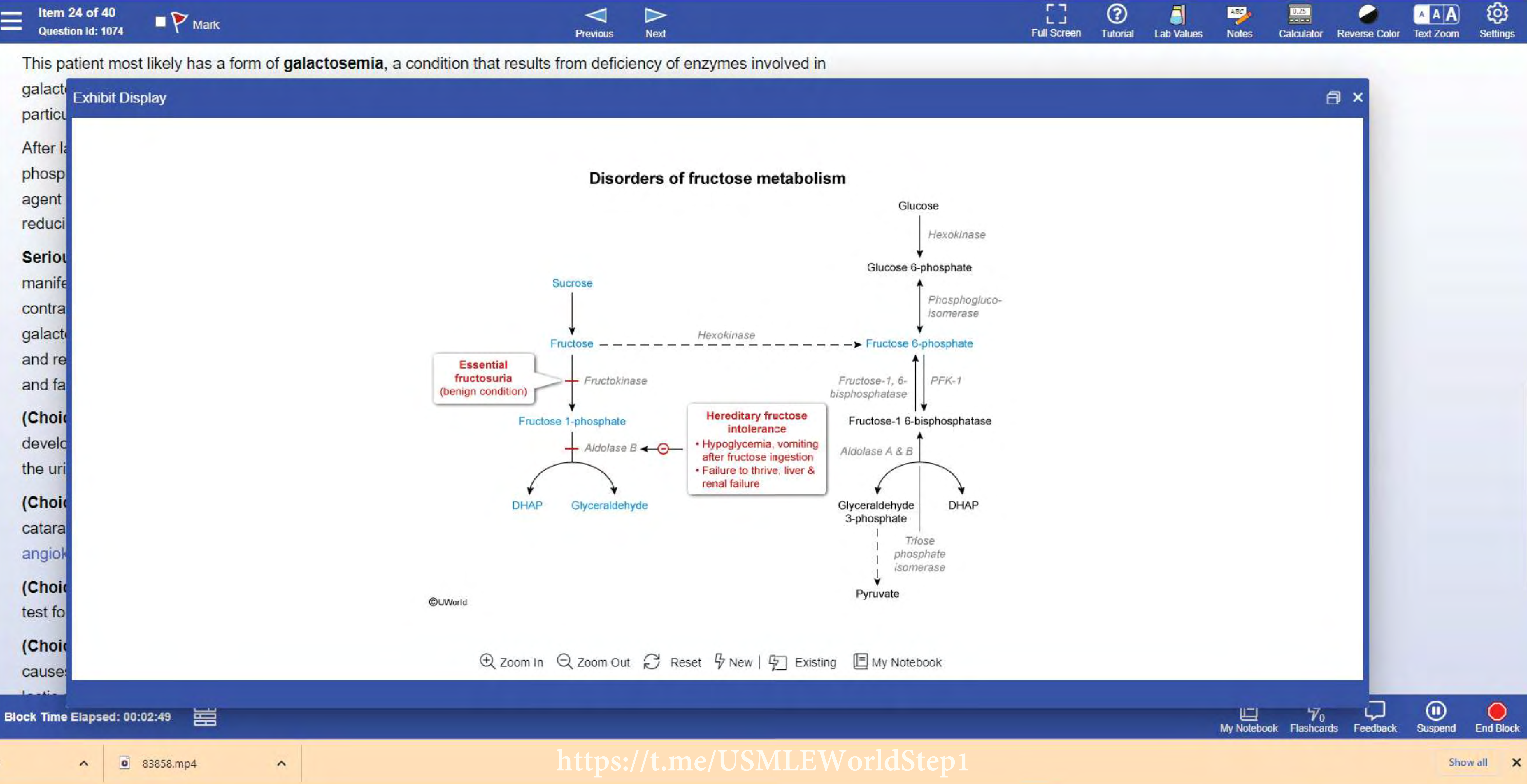
Item 24 of 40
Question Id: 1074
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Disorders of fructose metabolism

Glucose
Hexokinase
Glucose 6-phosphate
Phosphogluco-isomerase
Sucrose
Fructose
Hexokinase
Fructose 6-phosphate
Essential fructosuria (benign condition)
Fructokinase
Fructose-1, 6-bisphosphatase
PFK-1
Fructose 1-phosphate
Hereditary fructose intolerance
• Hypoglycemia, vomiting after fructose ingestion
• Failure to thrive, liver & renal failure
Fructose-1 6-bisphosphatase
Aldolase B
Aldolase A & B
DHAP
Glyceraldehyde
Glyceraldehyde 3-phosphate
DHAP
Triose phosphate isomerase
Pyruvate

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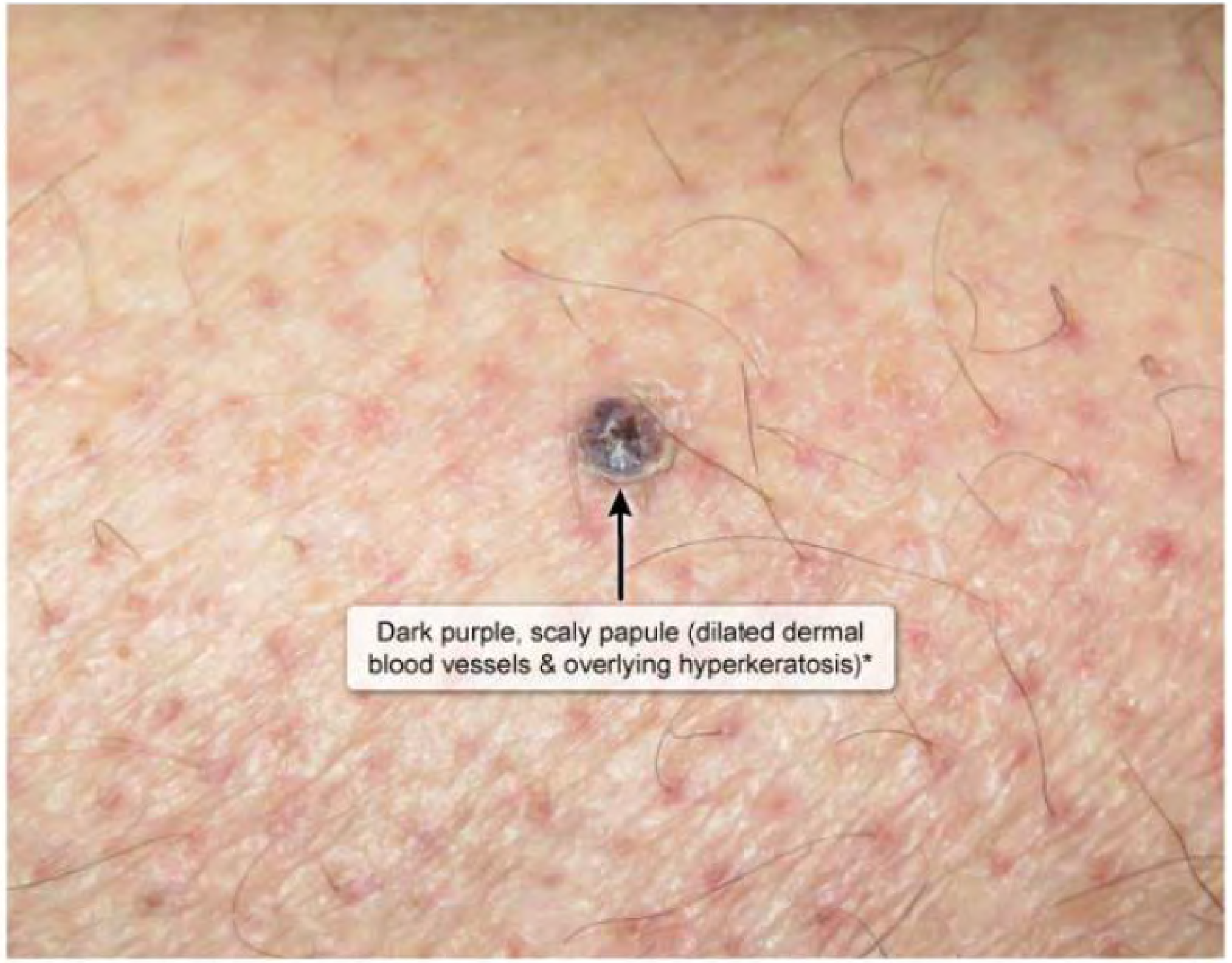
Angiokeratoma


Dark purple, scaly papule (dilated dermal blood vessels & overlying hyperkeratosis)*

*Numerous angiokeratomas seen in Fabry disease.

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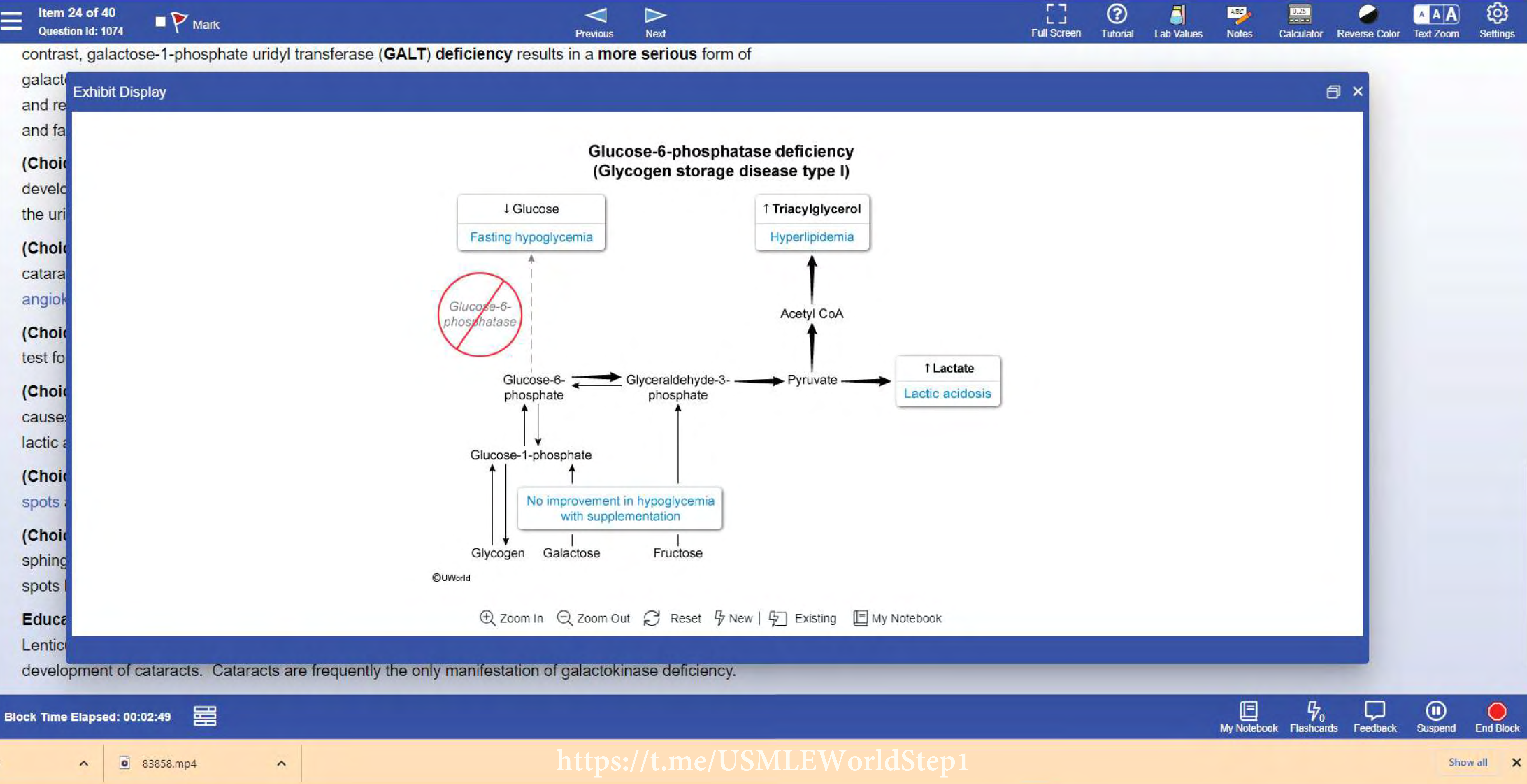
Item 24 of 40
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Glucose-6-phosphatase deficiency
(Glycogen storage disease type I)

↓ Glucose
Fasting hypoglycemia
↑ Triacylglycerol
Hyperlipidemia
Glucose-6-phosphatase
Acetyl CoA
Glucose-6-phosphate
Glyceraldehyde-3-phosphate
Pyruvate
↑ Lactate
Lactic acidosis
Glucose-1-phosphate
No improvement in hypoglycemia with supplementation
Glycogen
Galactose
Fructose
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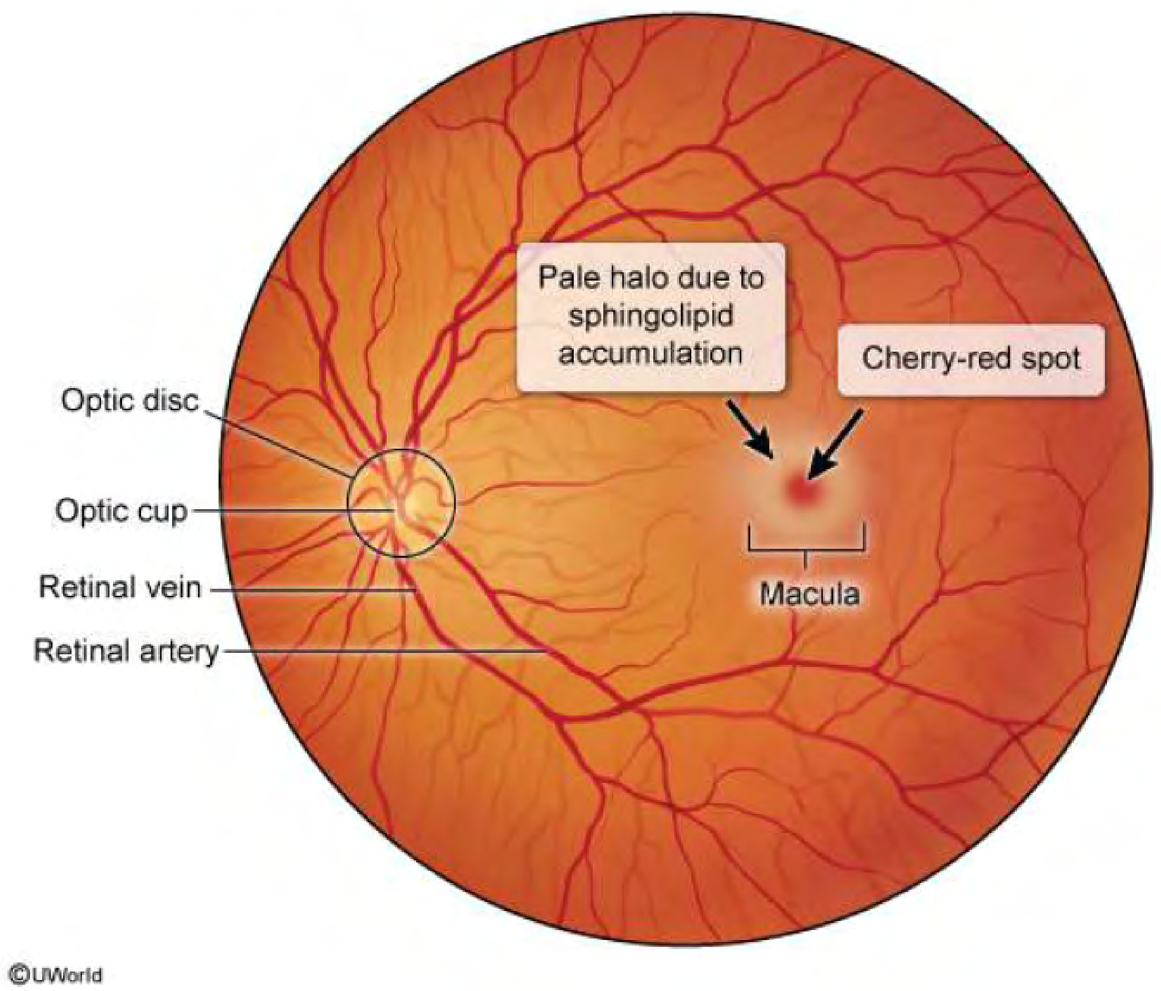
Cherry-red spot in lysosomal storage disease


Pale halo due to sphingolipid accumulation
Cherry-red spot
Optic disc
Optic cup
Retinal vein
Retinal artery
Macula

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development of cataracts. Cataracts are frequently the only manifestation of galactokinase deficiency.

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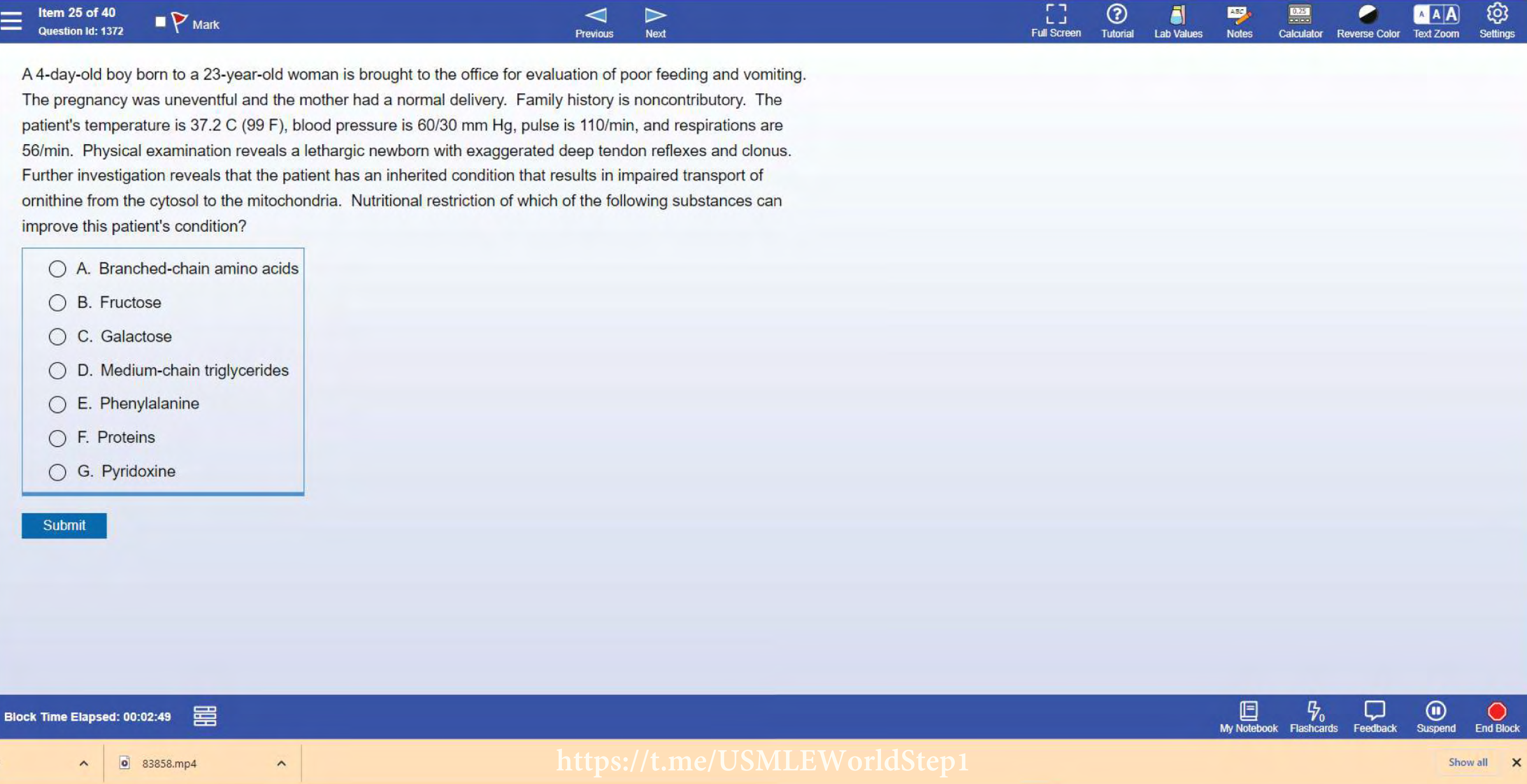
Item 25 of 40
Question Id: 1372
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 4-day-old boy born to a 23-year-old woman is brought to the office for evaluation of poor feeding and vomiting. The pregnancy was uneventful and the mother had a normal delivery. Family history is noncontributory. The patient's temperature is 37.2 C (99 F), blood pressure is 60/30 mm Hg, pulse is 110/min, and respirations are 56/min. Physical examination reveals a lethargic newborn with exaggerated deep tendon reflexes and clonus. Further investigation reveals that the patient has an inherited condition that results in impaired transport of ornithine from the cytosol to the mitochondria. Nutritional restriction of which of the following substances can improve this patient's condition?

- ○ A. Branched-chain amino acids
- ○ B. Fructose
- ○ C. Galactose
- ○ D. Medium-chain triglycerides
- ○ E. Phenylalanine
- ○ F. Proteins
- ○ G. Pyridoxine

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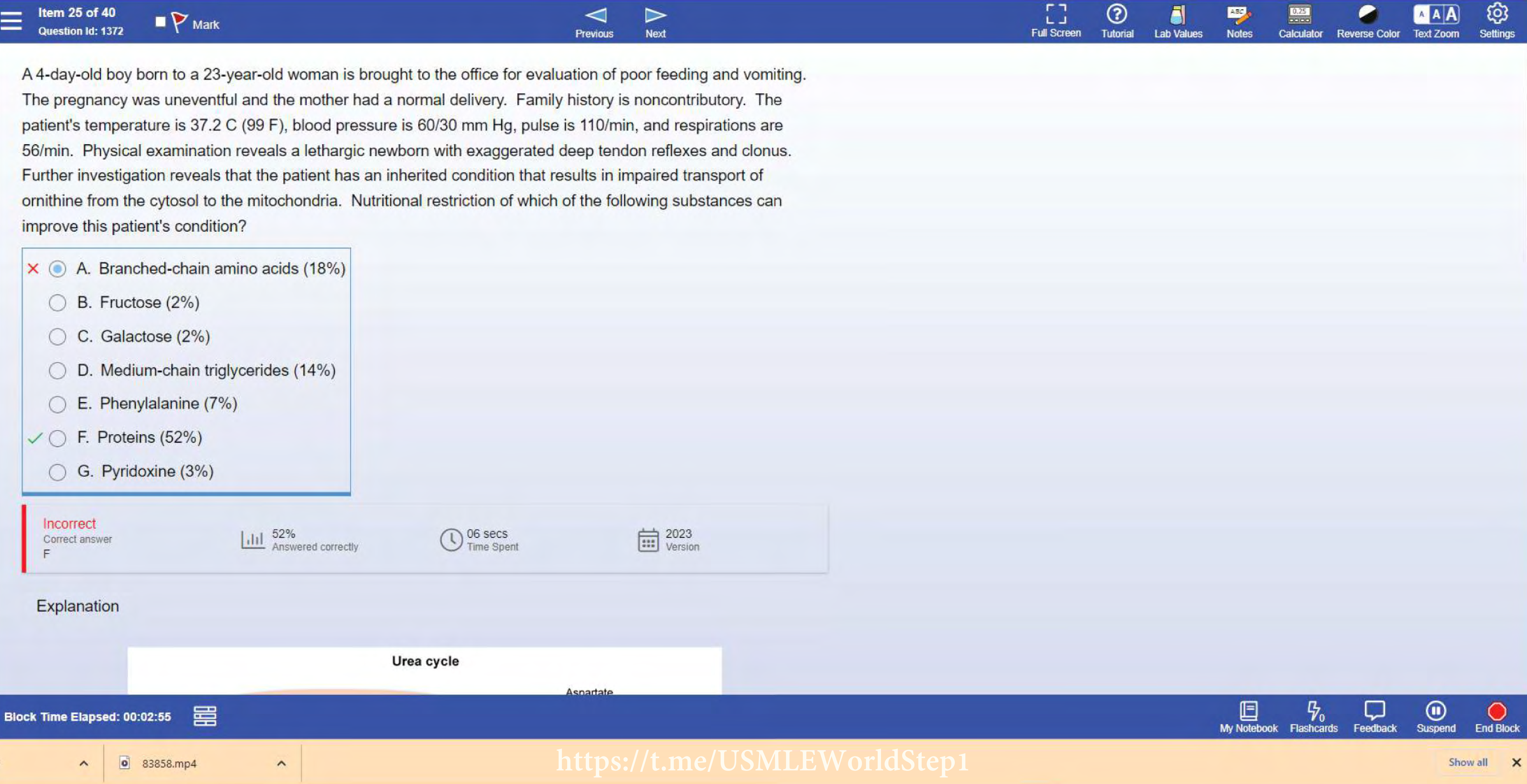
Item 25 of 40
Question Id: 1372
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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✗ ● A. Branched-chain amino acids (18%)
○ B. Fructose (2%)
○ C. Galactose (2%)
○ D. Medium-chain triglycerides (14%)
○ E. Phenylalanine (7%)
✓ ○ F. Proteins (52%)
○ G. Pyridoxine (3%)

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Correct answer
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52%
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Explanation

Urea cycle

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Feedback
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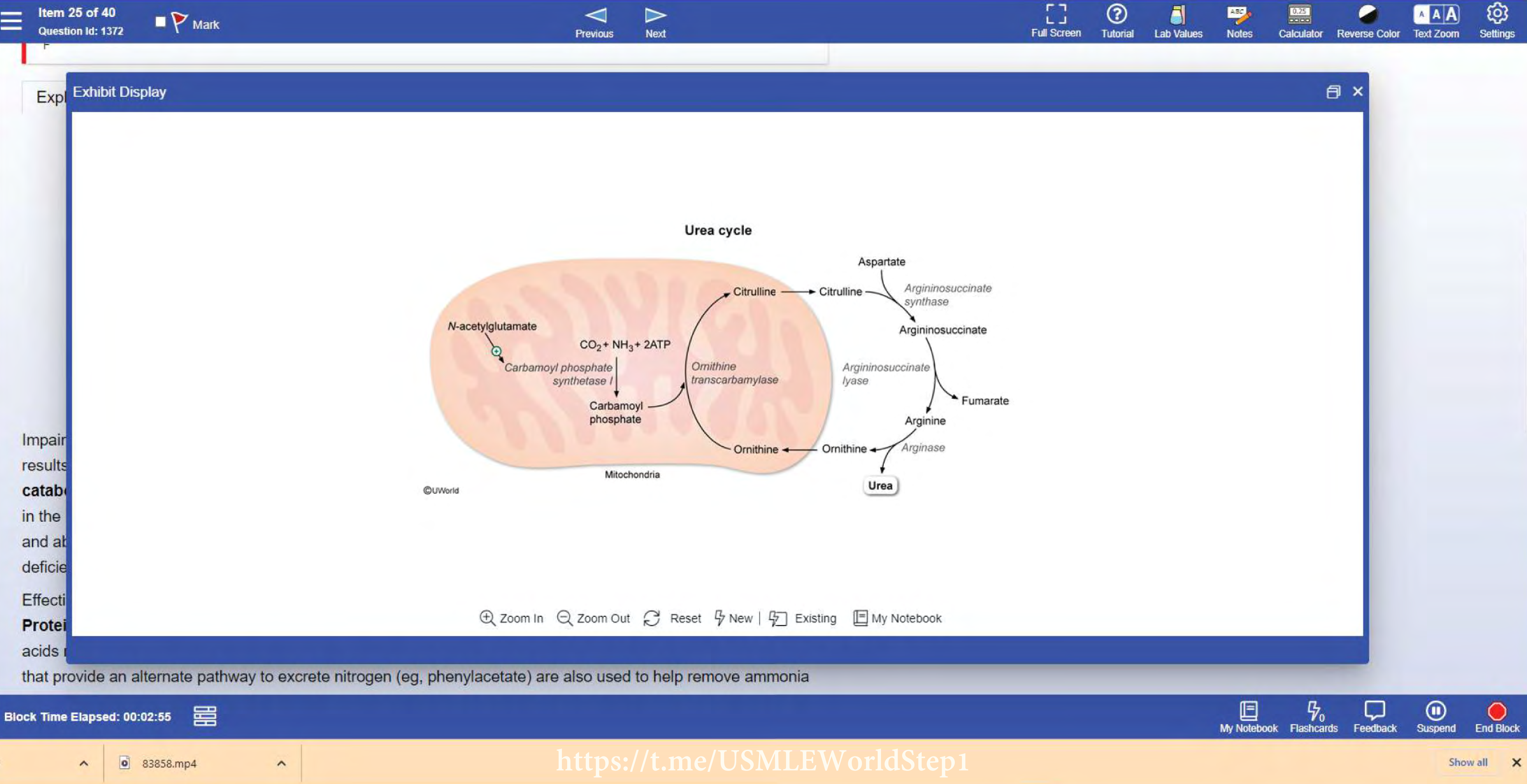
Item 25 of 40
Question Id: 1372
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Urea cycle
N-acetylglutamate
CO$_2$ + NH$_3$ + 2ATP
Carbamoyl phosphate synthetase I
Carbamoyl phosphate
Ornithine transcarbamylase
Citrulline
Ornithine
Mitochondria
Citrulline
Aspartate
Argininosuccinate synthase
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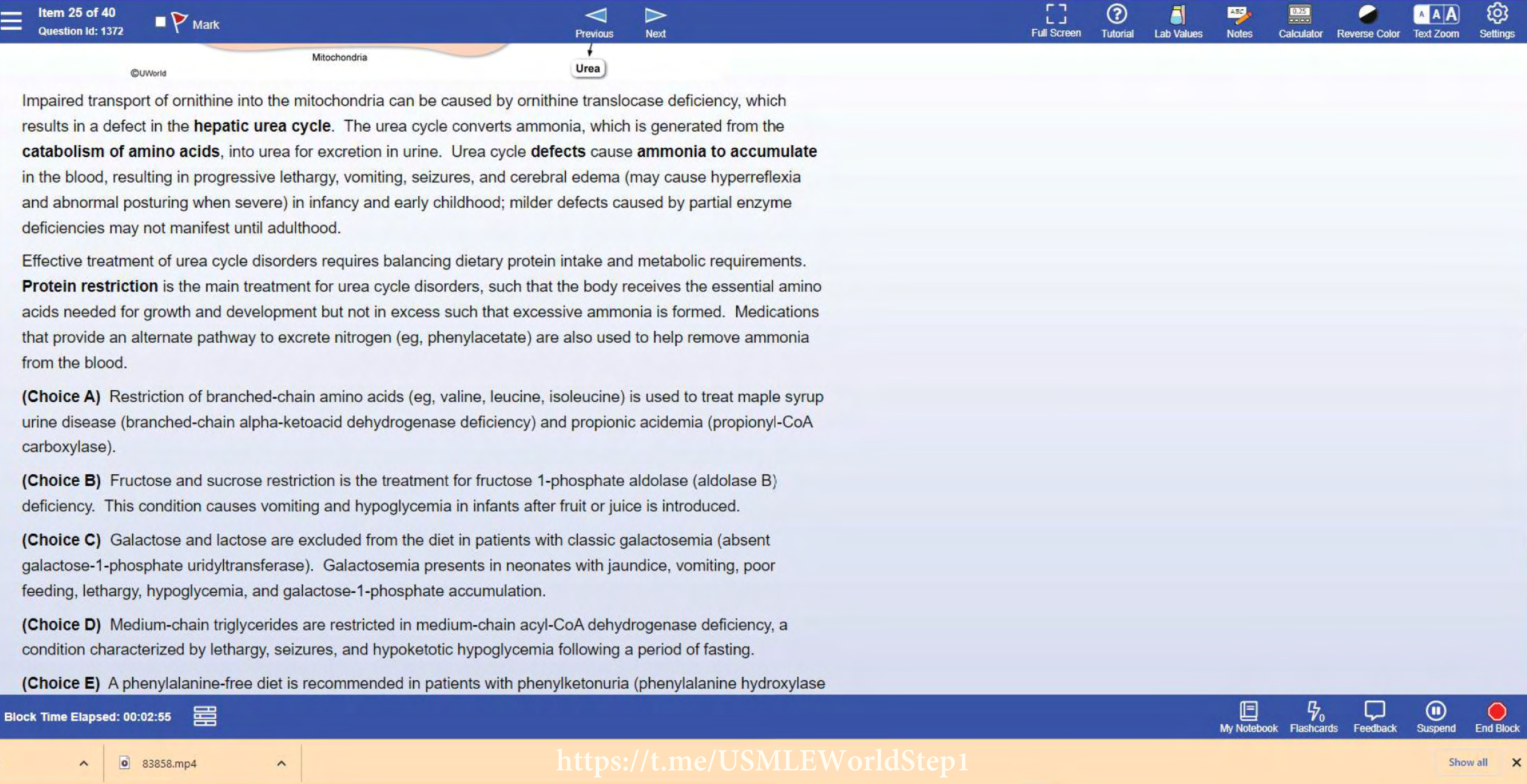
acids
that provide an alternate pathway to excrete nitrogen (eg, phenylacetate) are also used to help remove ammonia


Item 25 of 40
Question Id: 1372
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Mitochondria
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Impaired transport of ornithine into the mitochondria can be caused by ornithine translocase deficiency, which results in a defect in the **hepatic urea cycle**. The urea cycle converts ammonia, which is generated from the **catabolism of amino acids**, into urea for excretion in urine. Urea cycle **defects** cause **ammonia to accumulate** in the blood, resulting in progressive lethargy, vomiting, seizures, and cerebral edema (may cause hyperreflexia and abnormal posturing when severe) in infancy and early childhood; milder defects caused by partial enzyme deficiencies may not manifest until adulthood.

Effective treatment of urea cycle disorders requires balancing dietary protein intake and metabolic requirements. **Protein restriction** is the main treatment for urea cycle disorders, such that the body receives the essential amino acids needed for growth and development but not in excess such that excessive ammonia is formed. Medications that provide an alternate pathway to excrete nitrogen (eg, phenylacetate) are also used to help remove ammonia from the blood.

(Choice A) Restriction of branched-chain amino acids (eg, valine, leucine, isoleucine) is used to treat maple syrup urine disease (branched-chain alpha-ketoacid dehydrogenase deficiency) and propionic acidemia (propionyl-CoA carboxylase).

(Choice B) Fructose and sucrose restriction is the treatment for fructose 1-phosphate aldolase (aldolase B) deficiency. This condition causes vomiting and hypoglycemia in infants after fruit or juice is introduced.

(Choice C) Galactose and lactose are excluded from the diet in patients with classic galactosemia (absent galactose-1-phosphate uridyltransferase). Galactosemia presents in neonates with jaundice, vomiting, poor feeding, lethargy, hypoglycemia, and galactose-1-phosphate accumulation.

(Choice D) Medium-chain triglycerides are restricted in medium-chain acyl-CoA dehydrogenase deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period of fasting.

(Choice E) A phenylalanine-free diet is recommended in patients with phenylketonuria (phenylalanine hydroxylase

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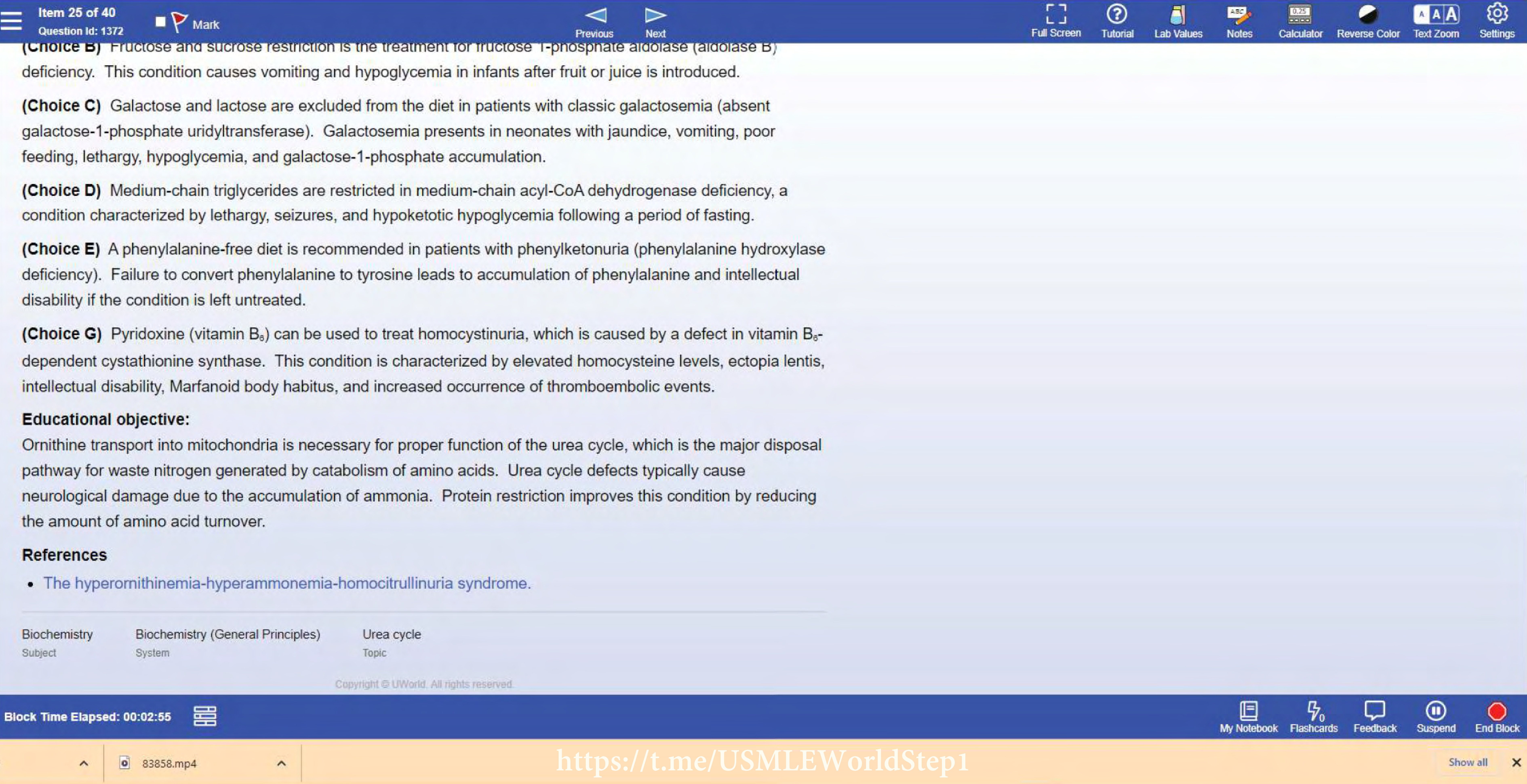

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(Choice D) Medium-chain triglycerides are restricted in medium-chain acyl-CoA dehydrogenase deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period of fasting.

(Choice E) A phenylalanine-free diet is recommended in patients with phenylketonuria (phenylalanine hydroxylase deficiency). Failure to convert phenylalanine to tyrosine leads to accumulation of phenylalanine and intellectual disability if the condition is left untreated.

(Choice G) Pyridoxine (vitamin B_6) can be used to treat homocystinuria, which is caused by a defect in vitamin B_6-dependent cystathionine synthase. This condition is characterized by elevated homocysteine levels, ectopia lentis, intellectual disability, Marfanoid body habitus, and increased occurrence of thromboembolic events.

Educational objective:

Ornithine transport into mitochondria is necessary for proper function of the urea cycle, which is the major disposal pathway for waste nitrogen generated by catabolism of amino acids. Urea cycle defects typically cause neurological damage due to the accumulation of ammonia. Protein restriction improves this condition by reducing the amount of amino acid turnover.

References

- The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.

Biochemistry	Biochemistry (General Principles)	Urea cycle
Subject	System	Topic

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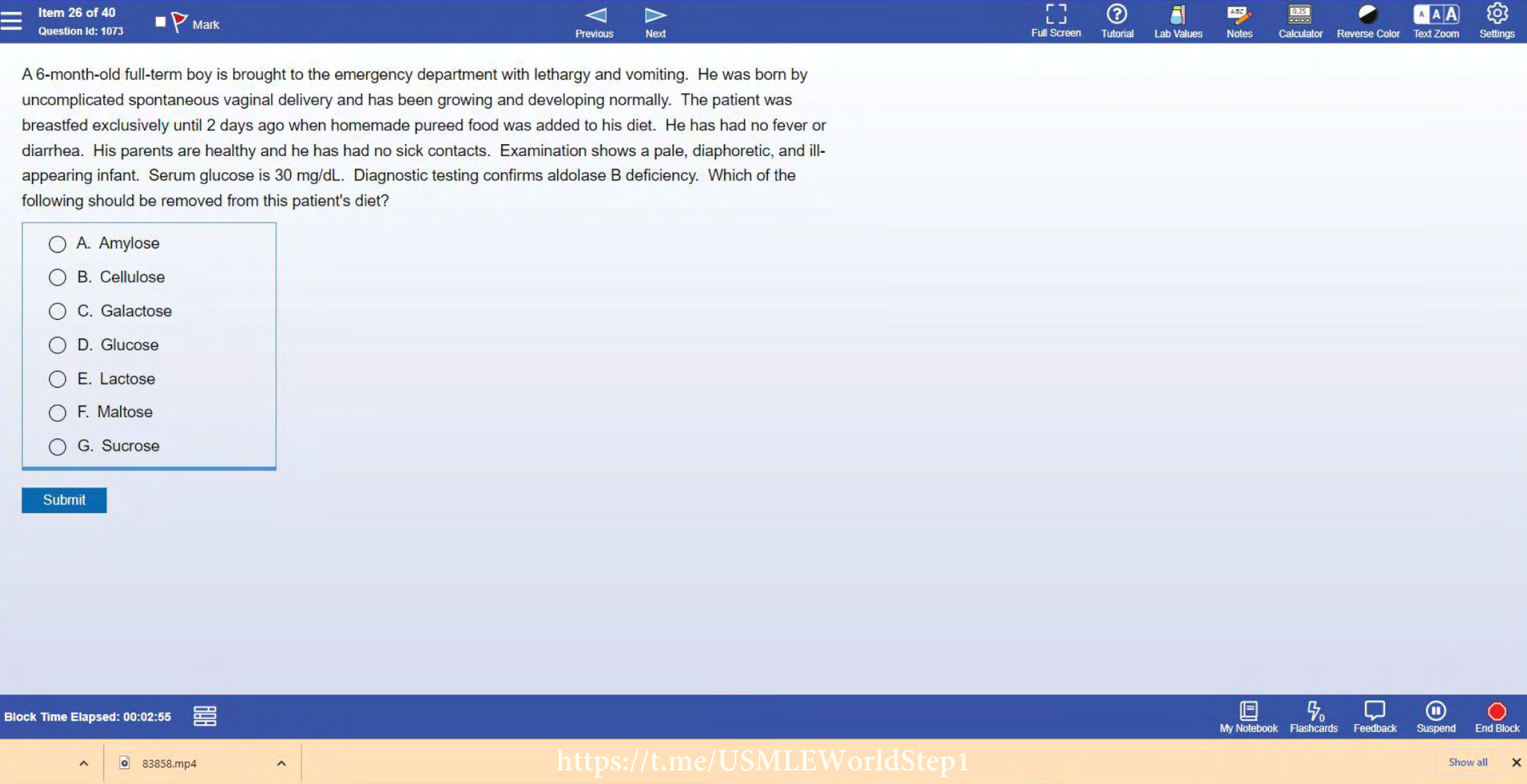
Item 26 of 40
Question Id: 1073
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:02:55
My Notebook
Flashcards
Feedback
Suspend
End Block
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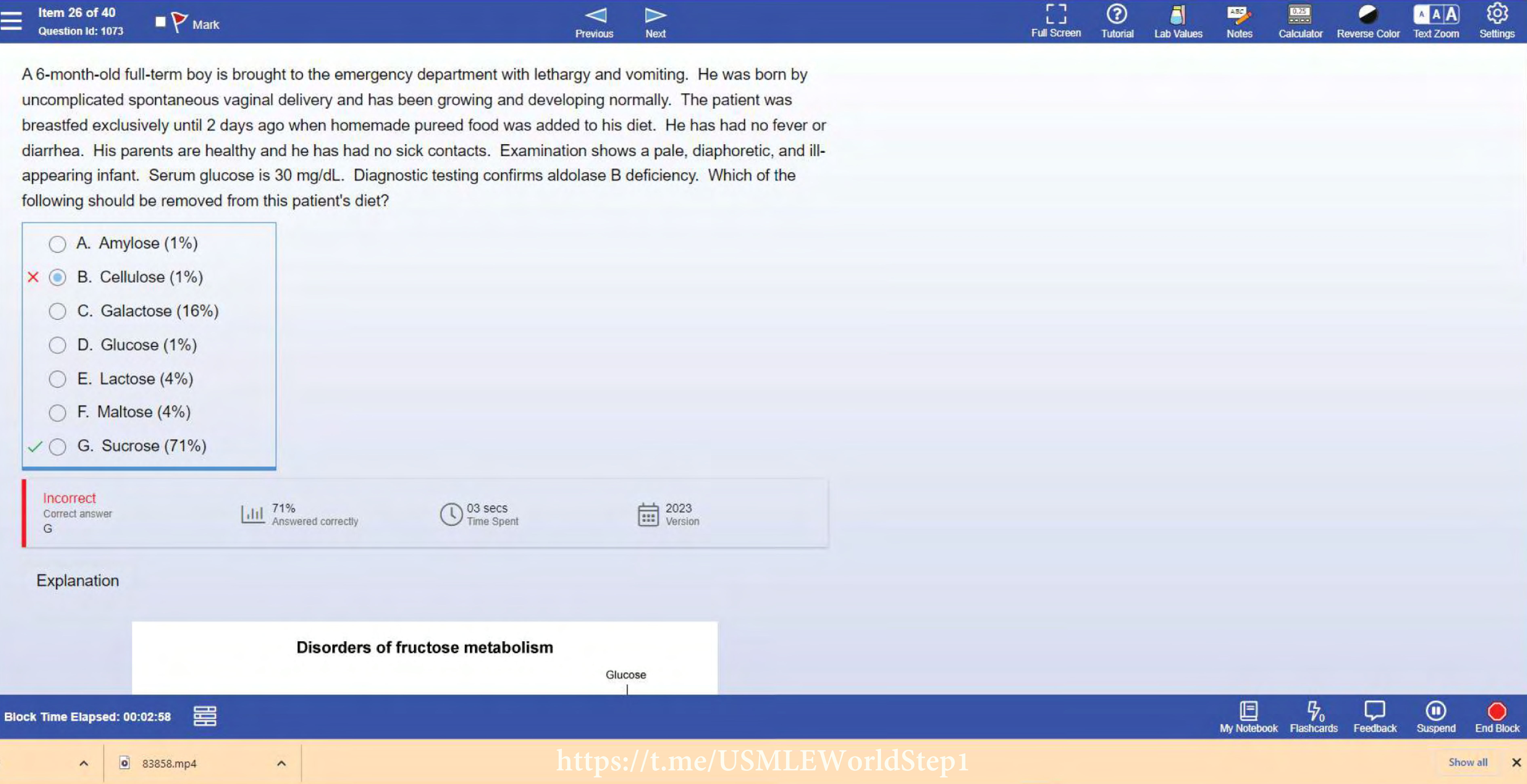
Show all

A 6-month-old full-term boy is brought to the emergency department with lethargy and vomiting. He was born by uncomplicated spontaneous vaginal delivery and has been growing and developing normally. The patient was breastfed exclusively until 2 days ago when homemade pureed food was added to his diet. He has had no fever or diarrhea. His parents are healthy and he has had no sick contacts. Examination shows a pale, diaphoretic, and ill-appearing infant. Serum glucose is 30 mg/dL. Diagnostic testing confirms aldolase B deficiency. Which of the following should be removed from this patient's diet?

○ A. Amylose
○ B. Cellulose
○ C. Galactose
○ D. Glucose
○ E. Lactose
○ F. Maltose
○ G. Sucrose


Item 26 of 40
Question Id: 1073
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 6-month-old full-term boy is brought to the emergency department with lethargy and vomiting. He was born by uncomplicated spontaneous vaginal delivery and has been growing and developing normally. The patient was breastfed exclusively until 2 days ago when homemade pureed food was added to his diet. He has had no fever or diarrhea. His parents are healthy and he has had no sick contacts. Examination shows a pale, diaphoretic, and ill-appearing infant. Serum glucose is 30 mg/dL. Diagnostic testing confirms aldolase B deficiency. Which of the following should be removed from this patient's diet?

○ A. Amylose (1%)
✗ ● B. Cellulose (1%)
○ C. Galactose (16%)
○ D. Glucose (1%)
○ E. Lactose (4%)
○ F. Maltose (4%)
✓ ○ G. Sucrose (71%)

Incorrect
Correct answer
G

71%
Answered correctly

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Explanation

Disorders of fructose metabolism

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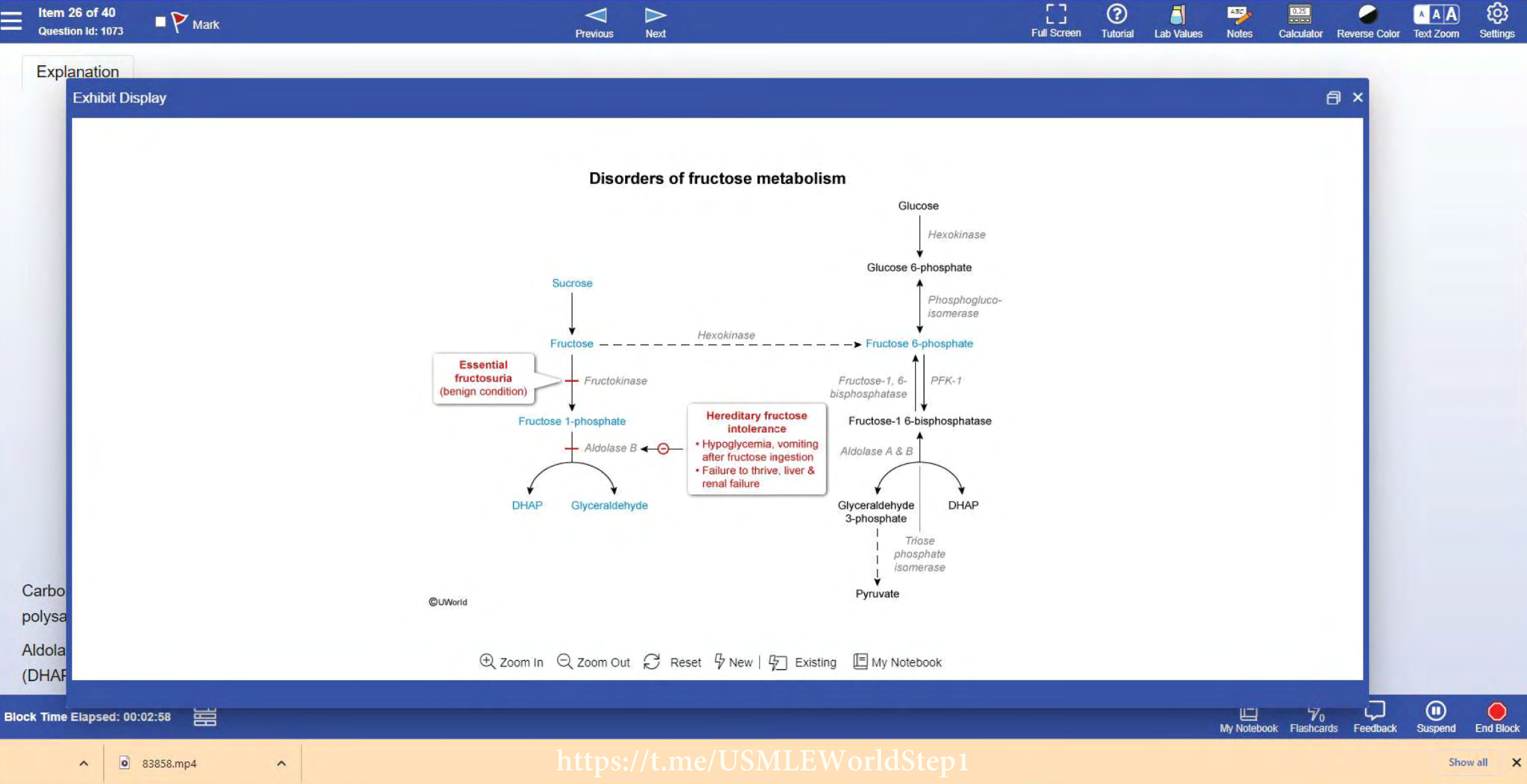
Item 26 of 40
Question Id: 1073
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display

Disorders of fructose metabolism

Glucose
Hexokinase
Glucose 6-phosphate
Phosphogluco-isomerase
Sucrose
Fructose
Hexokinase
Fructose 6-phosphate
Fructokinase
Fructose-1, 6-bisphosphatase
PFK-1
Fructose 1-phosphate
Fructose-1 6-bisphosphatase
Aldolase B
Aldolase A & B
DHAP
Glyceraldehyde
Glyceraldehyde 3-phosphate
DHAP
Triose phosphate isomerase
Pyruvate

Essential fructosuria
(benign condition)

Hereditary fructose intolerance
- Hypoglycemia, vomiting after fructose ingestion
- Failure to thrive, liver & renal failure

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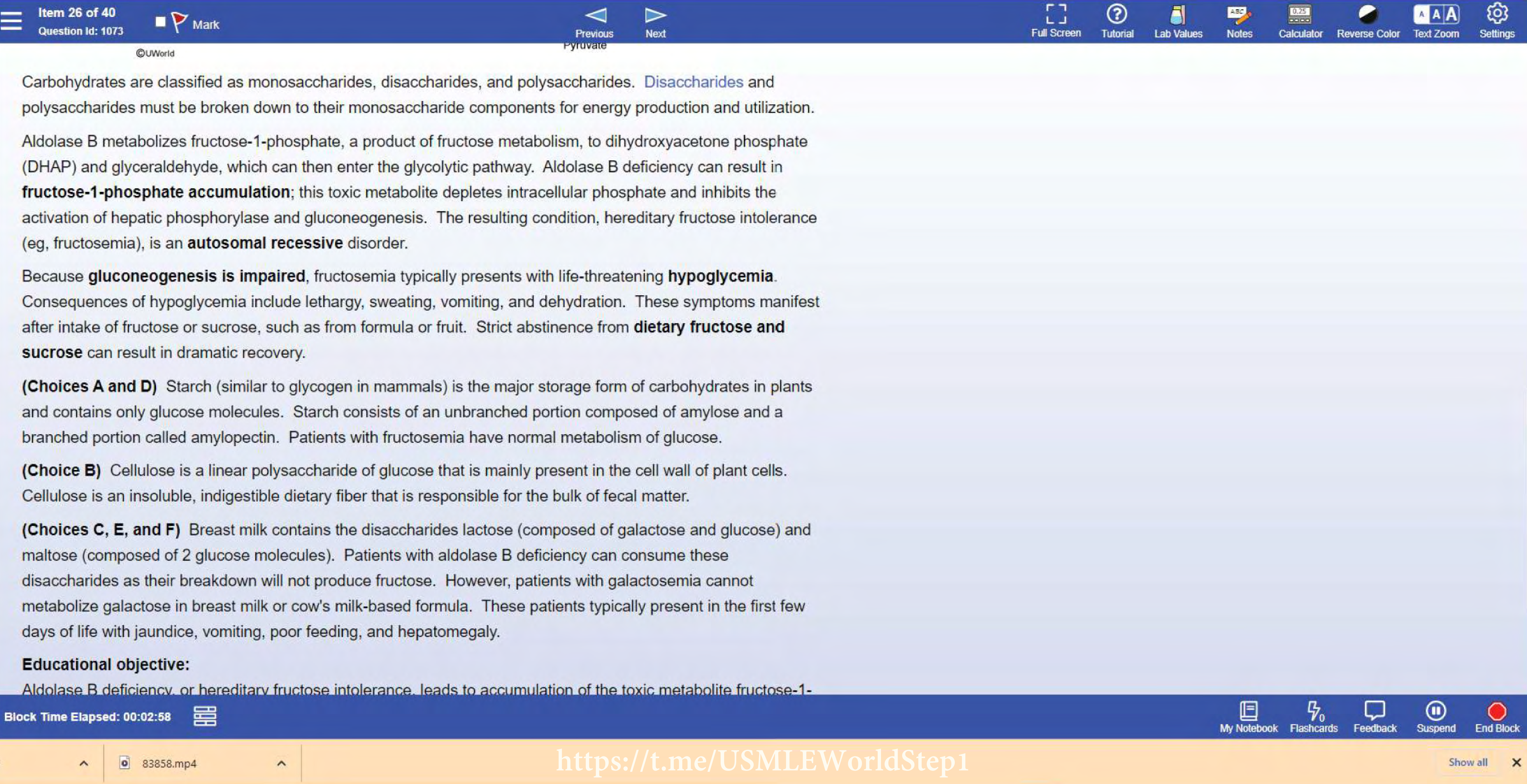


Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides. Disaccharides and polysaccharides must be broken down to their monosaccharide components for energy production and utilization.

Aldolase B metabolizes fructose-1-phosphate, a product of fructose metabolism, to dihydroxyacetone phosphate (DHAP) and glyceraldehyde, which can then enter the glycolytic pathway. Aldolase B deficiency can result in **fructose-1-phosphate accumulation**; this toxic metabolite depletes intracellular phosphate and inhibits the activation of hepatic phosphorylase and gluconeogenesis. The resulting condition, hereditary fructose intolerance (eg, fructosemia), is an **autosomal recessive** disorder.

Because **gluconeogenesis is impaired**, fructosemia typically presents with life-threatening **hypoglycemia**. Consequences of hypoglycemia include lethargy, sweating, vomiting, and dehydration. These symptoms manifest after intake of fructose or sucrose, such as from formula or fruit. Strict abstinence from **dietary fructose and sucrose** can result in dramatic recovery.

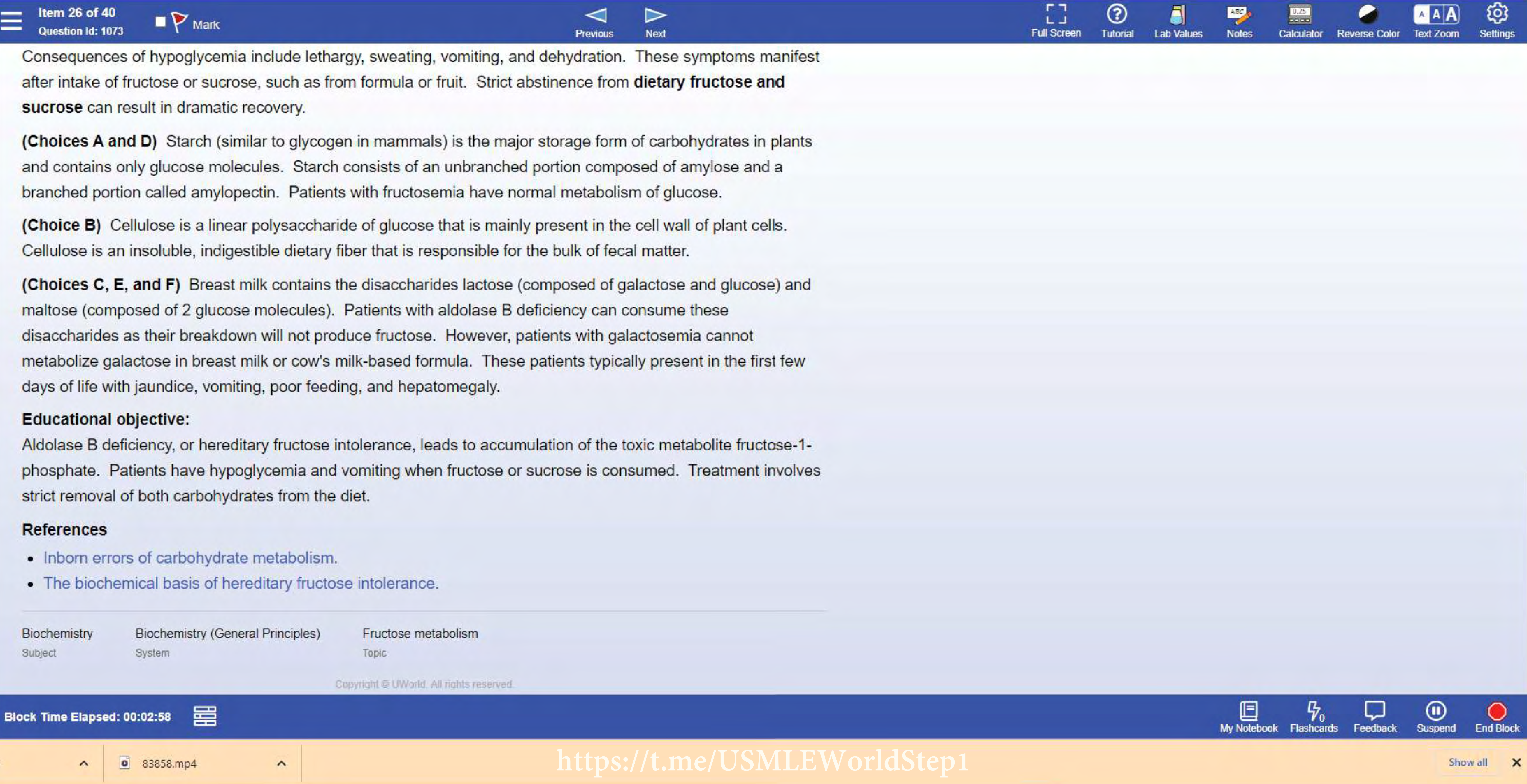
(Choices A and D) Starch (similar to glycogen in mammals) is the major storage form of carbohydrates in plants and contains only glucose molecules. Starch consists of an unbranched portion composed of amylose and a branched portion called amylopectin. Patients with fructosemia have normal metabolism of glucose.

(Choice B) Cellulose is a linear polysaccharide of glucose that is mainly present in the cell wall of plant cells. Cellulose is an insoluble, indigestible dietary fiber that is responsible for the bulk of fecal matter.

(Choices C, E, and F) Breast milk contains the disaccharides lactose (composed of galactose and glucose) and maltose (composed of 2 glucose molecules). Patients with aldolase B deficiency can consume these disaccharides as their breakdown will not produce fructose. However, patients with galactosemia cannot metabolize galactose in breast milk or cow's milk-based formula. These patients typically present in the first few days of life with jaundice, vomiting, poor feeding, and hepatomegaly.

Educational objective:

Aldolase B deficiency, or hereditary fructose intolerance, leads to accumulation of the toxic metabolite fructose-1-


Item 26 of 40
Question Id: 1073
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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Educational objective:

Aldolase B deficiency, or hereditary fructose intolerance, leads to accumulation of the toxic metabolite fructose-1-phosphate. Patients have hypoglycemia and vomiting when fructose or sucrose is consumed. Treatment involves strict removal of both carbohydrates from the diet.

References

- Inborn errors of carbohydrate metabolism.
- The biochemical basis of hereditary fructose intolerance.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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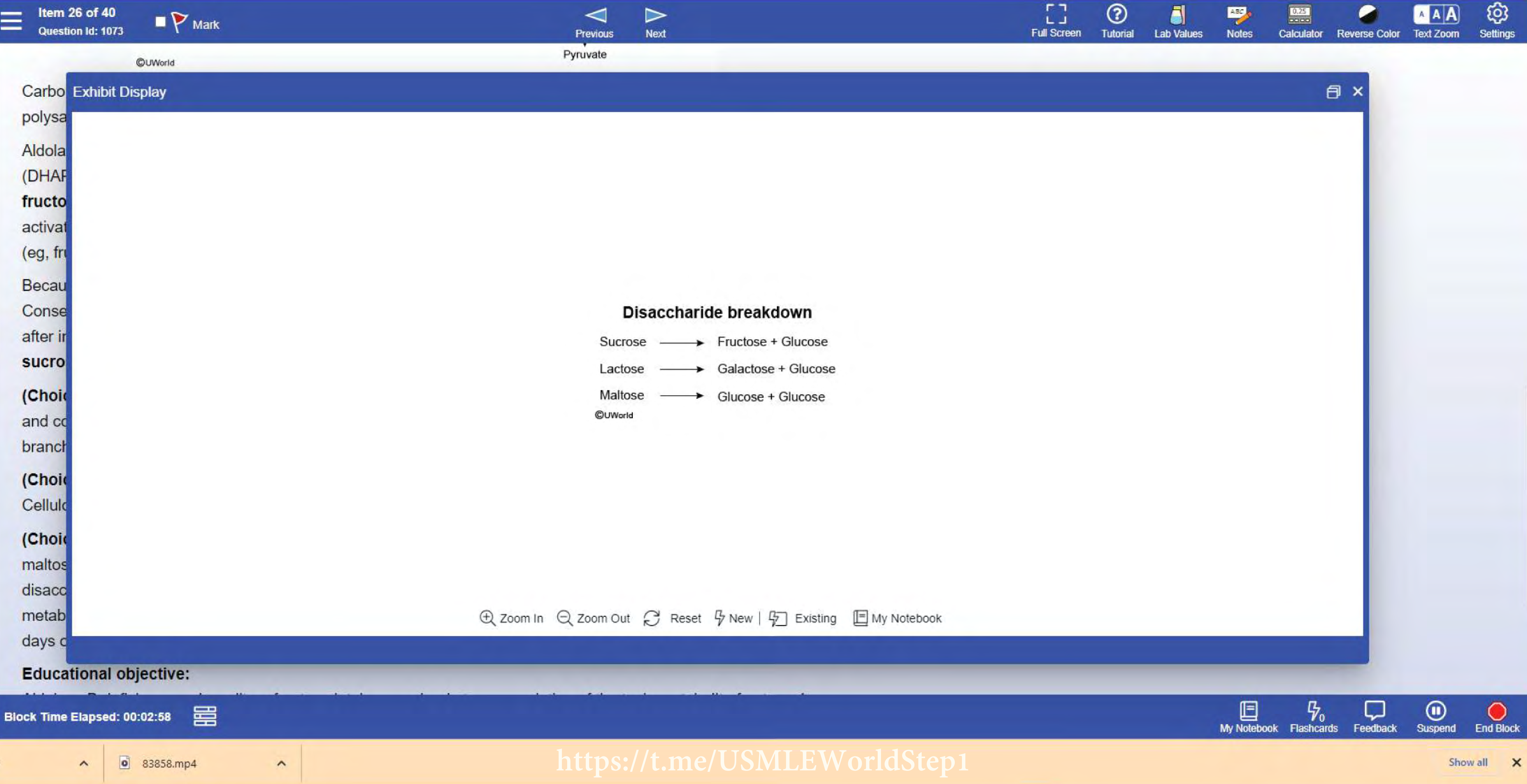
Item 26 of 40
Question Id: 1073
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Pyruvate
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Disaccharide breakdown

Sucrose → Fructose + Glucose

Lactose → Galactose + Glucose

Maltose → Glucose + Glucose

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Educational objective:

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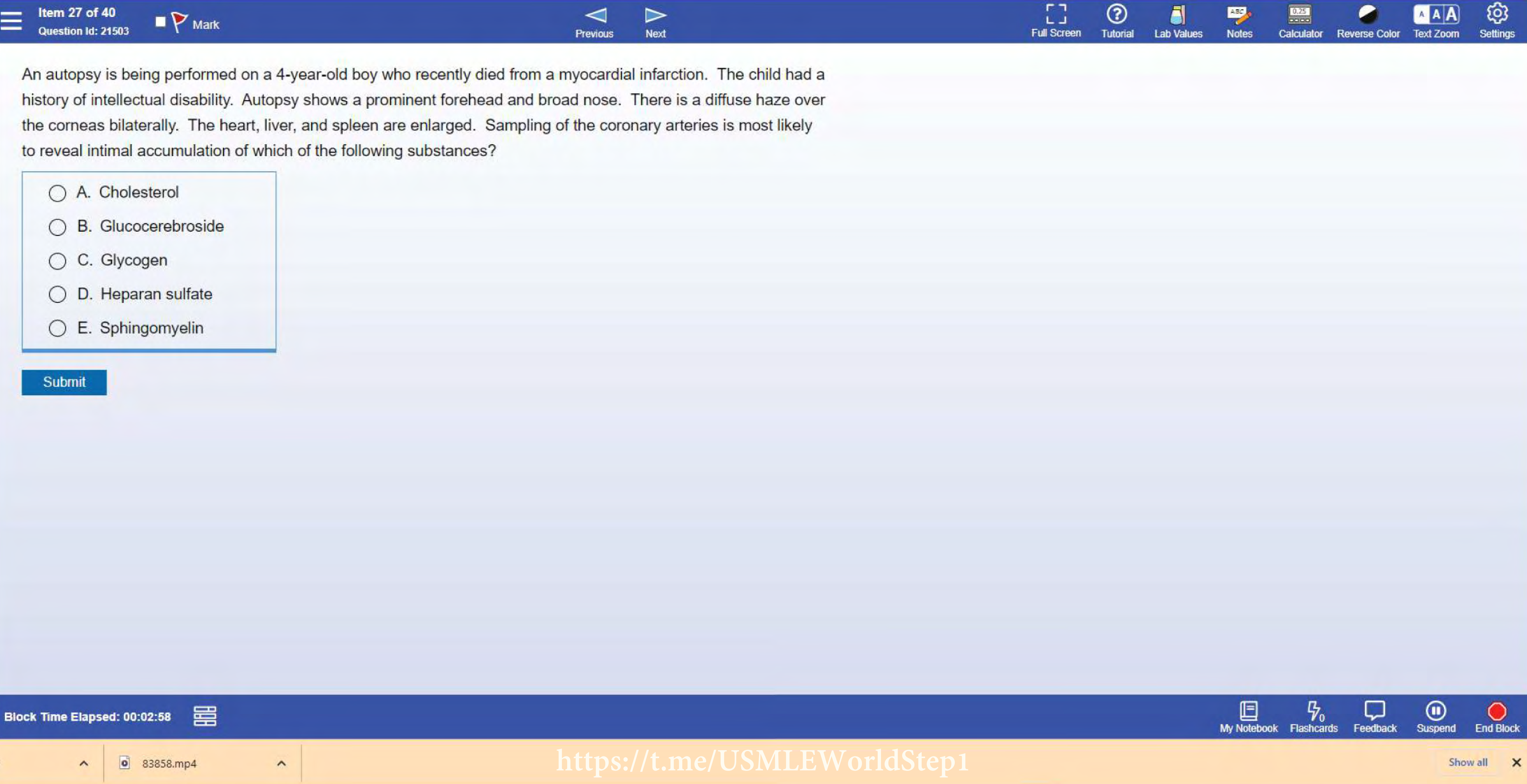
Item 27 of 40
Question Id: 21503
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An autopsy is being performed on a 4-year-old boy who recently died from a myocardial infarction. The child had a history of intellectual disability. Autopsy shows a prominent forehead and broad nose. There is a diffuse haze over the corneas bilaterally. The heart, liver, and spleen are enlarged. Sampling of the coronary arteries is most likely to reveal intimal accumulation of which of the following substances?

○ A. Cholesterol
○ B. Glucocerebroside
○ C. Glycogen
○ D. Heparan sulfate
○ E. Sphingomyelin

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Feedback
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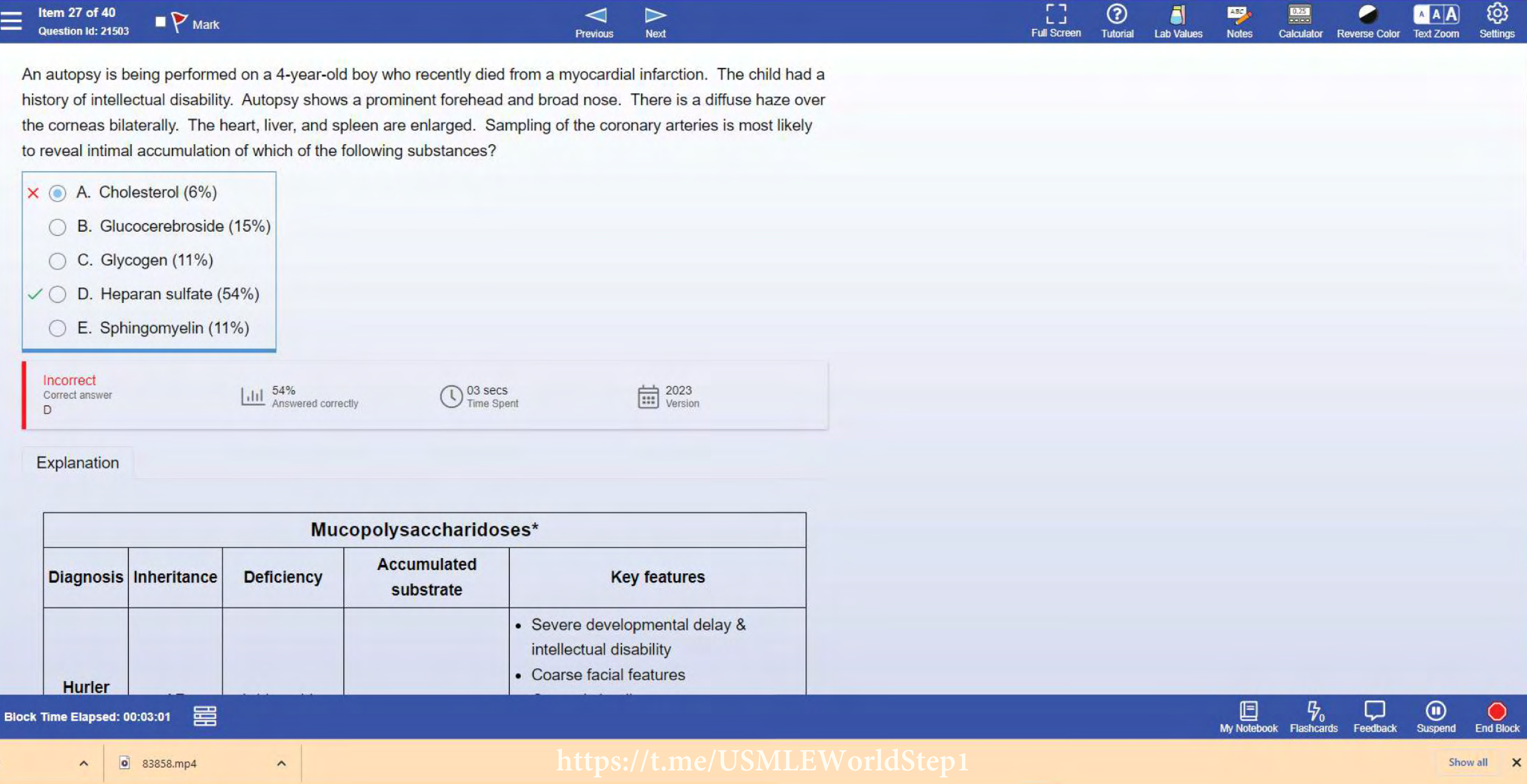
Item 27 of 40
Question Id: 21503
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Feedback
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- ✗ ● A. Cholesterol (6%)
- ○ B. Glucocerebroside (15%)
- ○ C. Glycogen (11%)
- ✓ ○ D. Heparan sulfate (54%)
- ○ E. Sphingomyelin (11%)

Incorrect
Correct answer
D

54%
Answered correctly

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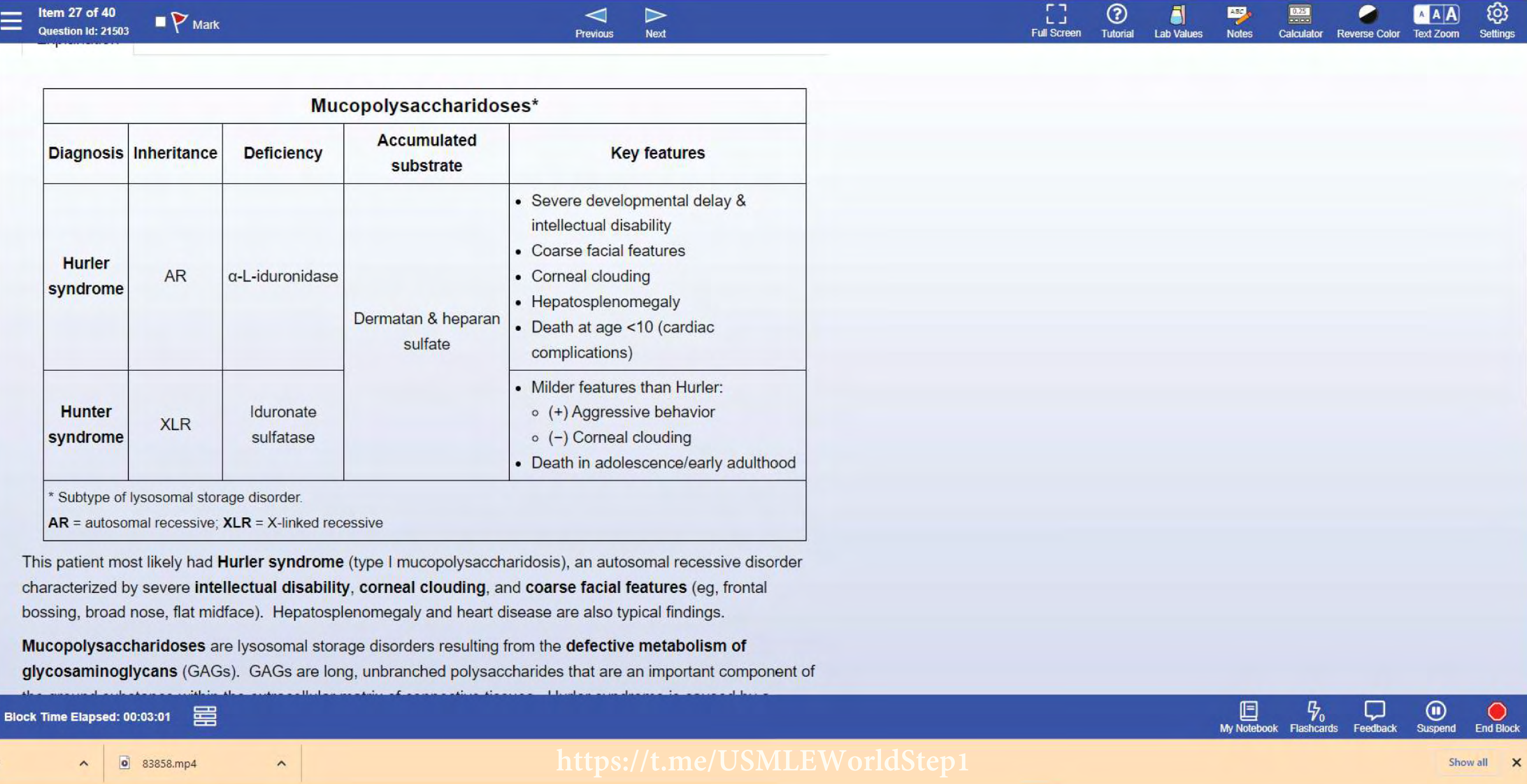
2023
Version

Explanation

Mucopolysaccharidoses*				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Hurler				• Severe developmental delay & intellectual disability • Coarse facial features


Item 27 of 40
Question Id: 21503
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:01
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Mucopolysaccharidoses*

Diagnosis	Inheritance	Deficiency	Accumulated substrate	Key features
Hurler syndrome	AR	α-L-iduronidase	Dermatan & heparan sulfate	• Severe developmental delay & intellectual disability • Coarse facial features • Corneal clouding • Hepatosplenomegaly • Death at age <10 (cardiac complications)

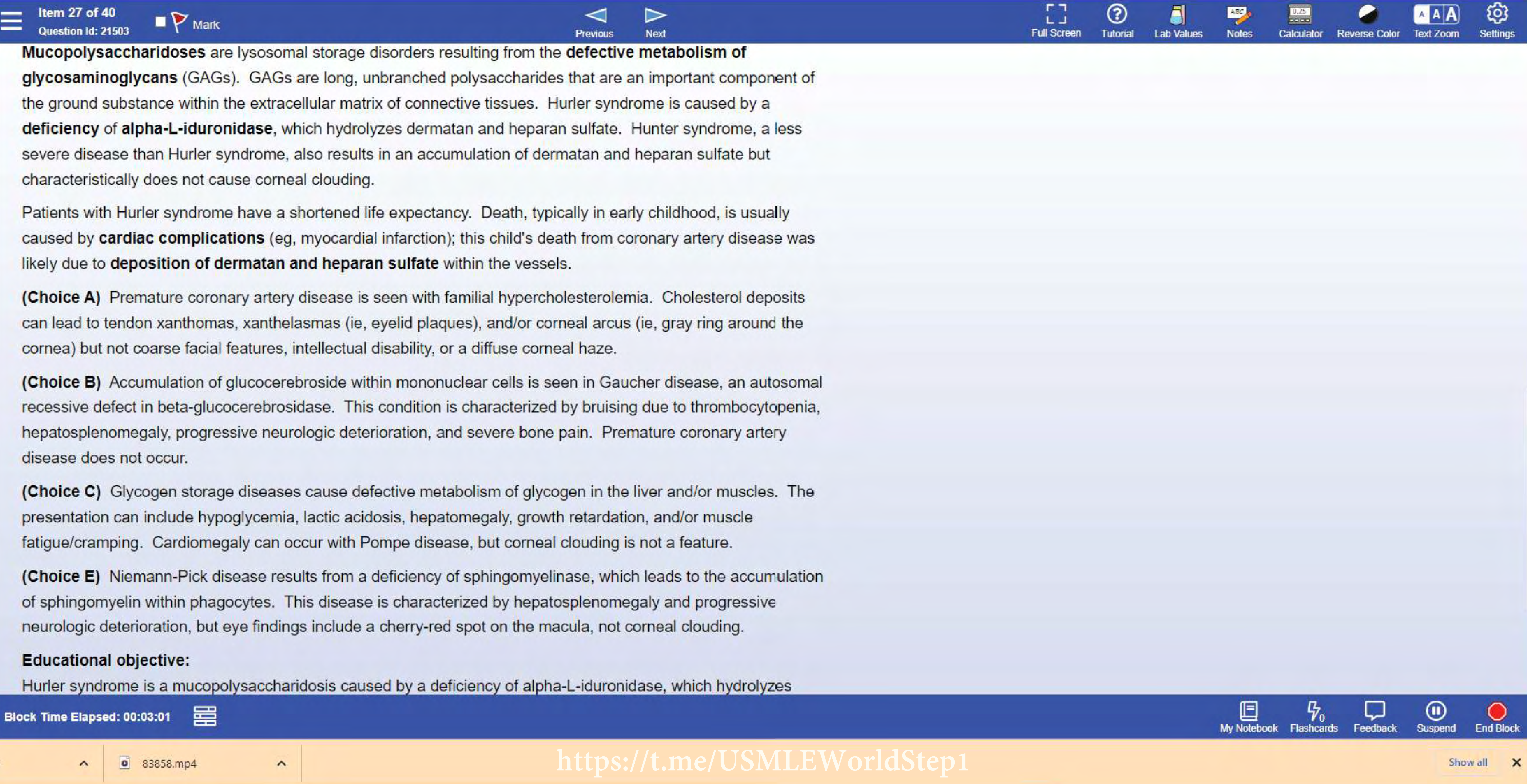
Hunter syndrome	XLR	Iduronate sulfatase		• Milder features than Hurler:
				  ○ (+) Aggressive behavior
				  ○ (−) Corneal clouding
				• Death in adolescence/early adulthood

* Subtype of lysosomal storage disorder.

AR = autosomal recessive; **XLR** = X-linked recessive

This patient most likely had **Hurler syndrome** (type I mucopolysaccharidosis), an autosomal recessive disorder characterized by severe **intellectual disability**, **corneal clouding**, and **coarse facial features** (eg, frontal bossing, broad nose, flat midface). Hepatosplenomegaly and heart disease are also typical findings.

Mucopolysaccharidoses are lysosomal storage disorders resulting from the **defective metabolism of glycosaminoglycans** (GAGs). GAGs are long, unbranched polysaccharides that are an important component of



Mucopolysaccharidoses are lysosomal storage disorders resulting from the **defective metabolism of glycosaminoglycans** (GAGs). GAGs are long, unbranched polysaccharides that are an important component of the ground substance within the extracellular matrix of connective tissues. Hurler syndrome is caused by a **deficiency** of **alpha-L-iduronidase**, which hydrolyzes dermatan and heparan sulfate. Hunter syndrome, a less severe disease than Hurler syndrome, also results in an accumulation of dermatan and heparan sulfate but characteristically does not cause corneal clouding.

Patients with Hurler syndrome have a shortened life expectancy. Death, typically in early childhood, is usually caused by **cardiac complications** (eg, myocardial infarction); this child's death from coronary artery disease was likely due to **deposition of dermatan and heparan sulfate** within the vessels.

(Choice A) Premature coronary artery disease is seen with familial hypercholesterolemia. Cholesterol deposits can lead to tendon xanthomas, xanthelasmas (ie, eyelid plaques), and/or corneal arcus (ie, gray ring around the cornea) but not coarse facial features, intellectual disability, or a diffuse corneal haze.

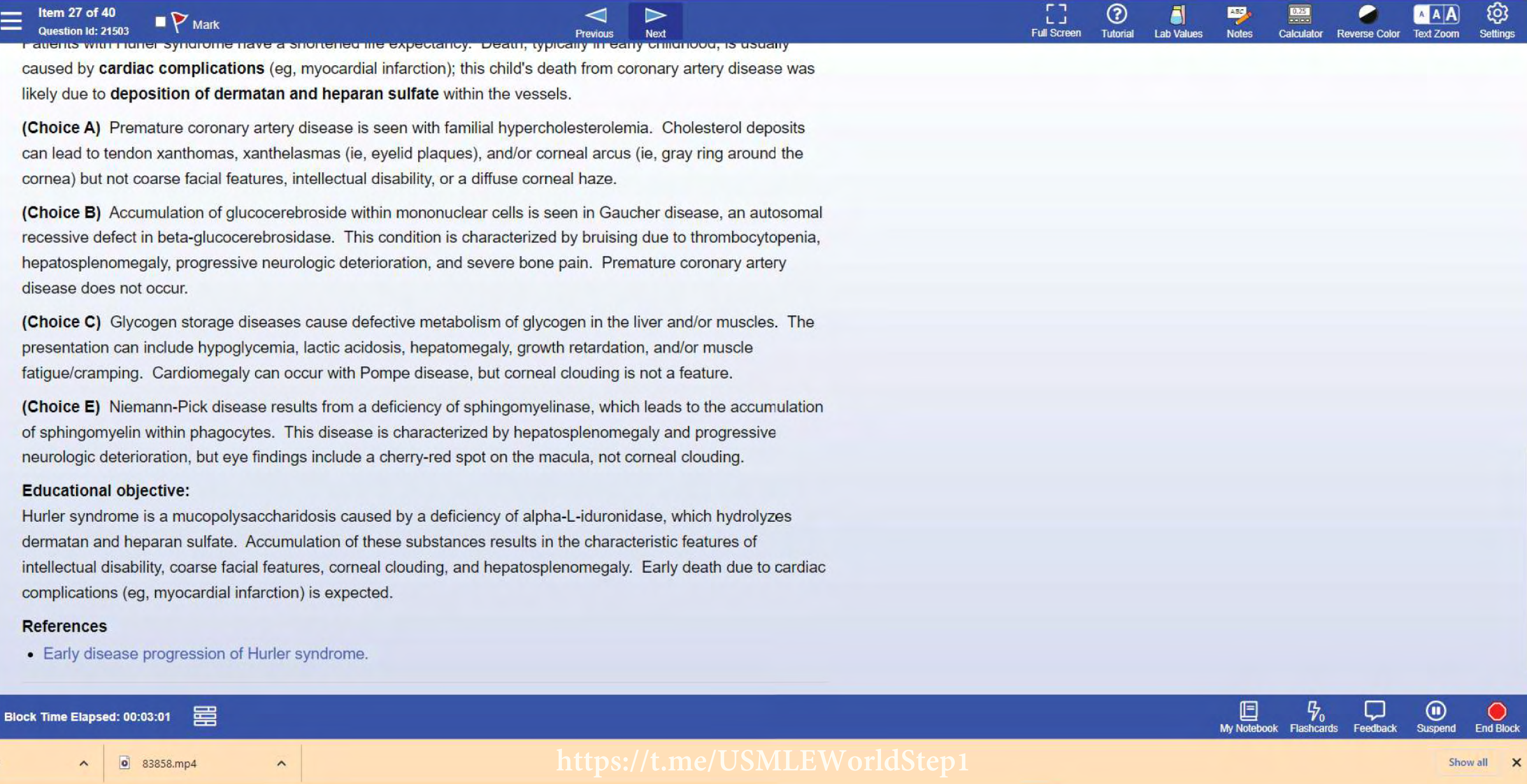
(Choice B) Accumulation of glucocerebroside within mononuclear cells is seen in Gaucher disease, an autosomal recessive defect in beta-glucocerebrosidase. This condition is characterized by bruising due to thrombocytopenia, hepatosplenomegaly, progressive neurologic deterioration, and severe bone pain. Premature coronary artery disease does not occur.

(Choice C) Glycogen storage diseases cause defective metabolism of glycogen in the liver and/or muscles. The presentation can include hypoglycemia, lactic acidosis, hepatomegaly, growth retardation, and/or muscle fatigue/cramping. Cardiomegaly can occur with Pompe disease, but corneal clouding is not a feature.

(Choice E) Niemann-Pick disease results from a deficiency of sphingomyelinase, which leads to the accumulation of sphingomyelin within phagocytes. This disease is characterized by hepatosplenomegaly and progressive neurologic deterioration, but eye findings include a cherry-red spot on the macula, not corneal clouding.

Educational objective:

Hurler syndrome is a mucopolysaccharidosis caused by a deficiency of alpha-L-iduronidase, which hydrolyzes



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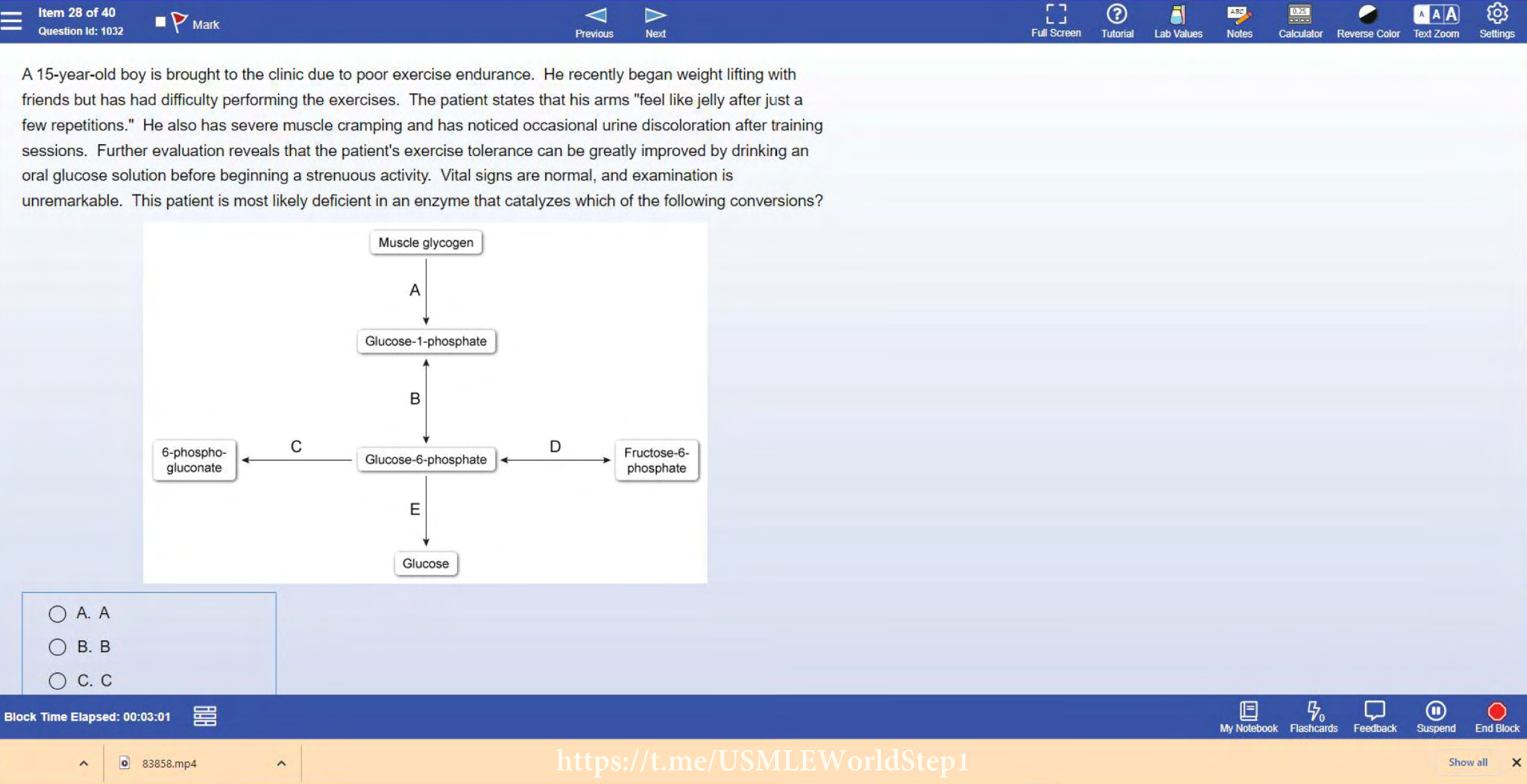
Educational objective:

Hurler syndrome is a mucopolysaccharidosis caused by a deficiency of alpha-L-iduronidase, which hydrolyzes dermatan and heparan sulfate. Accumulation of these substances results in the characteristic features of intellectual disability, coarse facial features, corneal clouding, and hepatosplenomegaly. Early death due to cardiac complications (eg, myocardial infarction) is expected.

References

- Early disease progression of Hurler syndrome.


Item 28 of 40
Question Id: 1032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Muscle glycogen
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Glucose-1-phosphate
B
6-phospho-gluconate
C
Glucose-6-phosphate
D
Fructose-6-phosphate
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My Notebook
Flashcards
Feedback
Suspend
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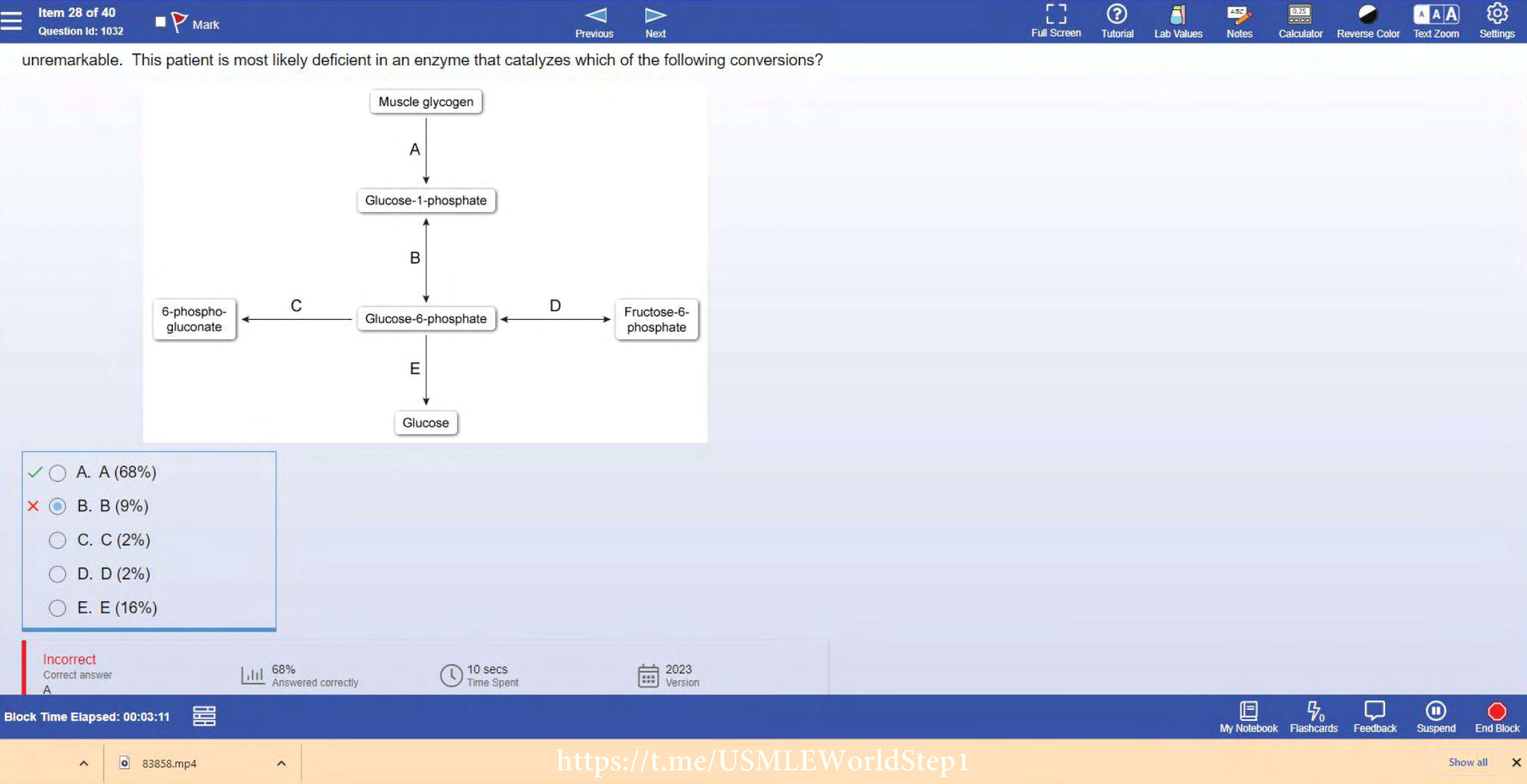
A 15-year-old boy is brought to the clinic due to poor exercise endurance. He recently began weight lifting with friends but has had difficulty performing the exercises. The patient states that his arms "feel like jelly after just a few repetitions." He also has severe muscle cramping and has noticed occasional urine discoloration after training sessions. Further evaluation reveals that the patient's exercise tolerance can be greatly improved by drinking an oral glucose solution before beginning a strenuous activity. Vital signs are normal, and examination is unremarkable. This patient is most likely deficient in an enzyme that catalyzes which of the following conversions?

○ A. A
○ B. B
○ C. C


Item 28 of 40
Question Id: 1032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Muscle glycogen
A
Glucose-1-phosphate
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6-phospho-gluconate
C
Glucose-6-phosphate
D
Fructose-6-phosphate
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Glucose
My Notebook
Flashcards
Feedback
Suspend
End Block
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unremarkable. This patient is most likely deficient in an enzyme that catalyzes which of the following conversions?

✓ ○ A. A (68%)

✗ ● B. B (9%)

○ C. C (2%)

○ D. D (2%)

○ E. E (16%)

Incorrect
Correct answer
A

68%
Answered correctly

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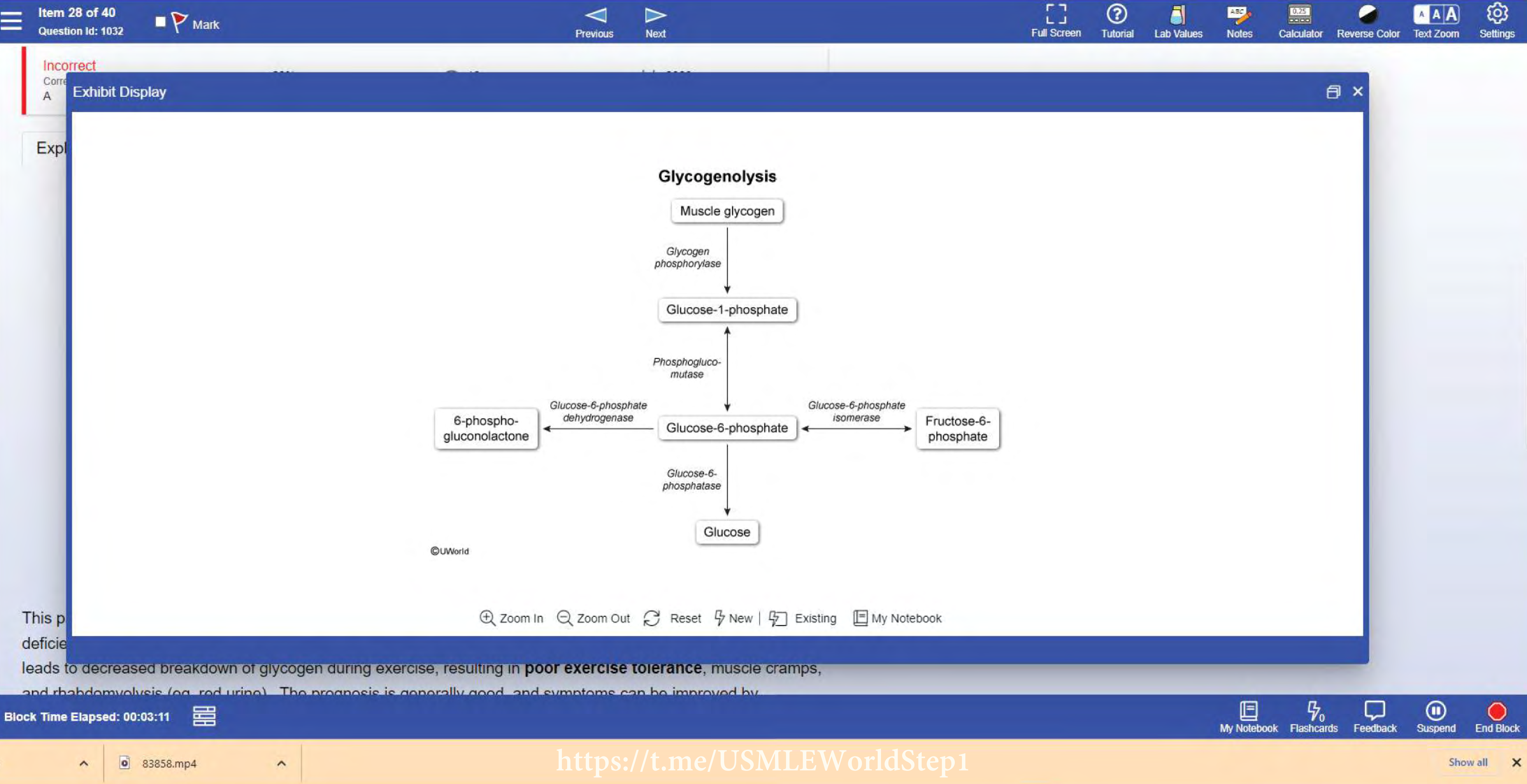

Item 28 of 40
Question Id: 1032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
Settings
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Phosphogluco-mutase
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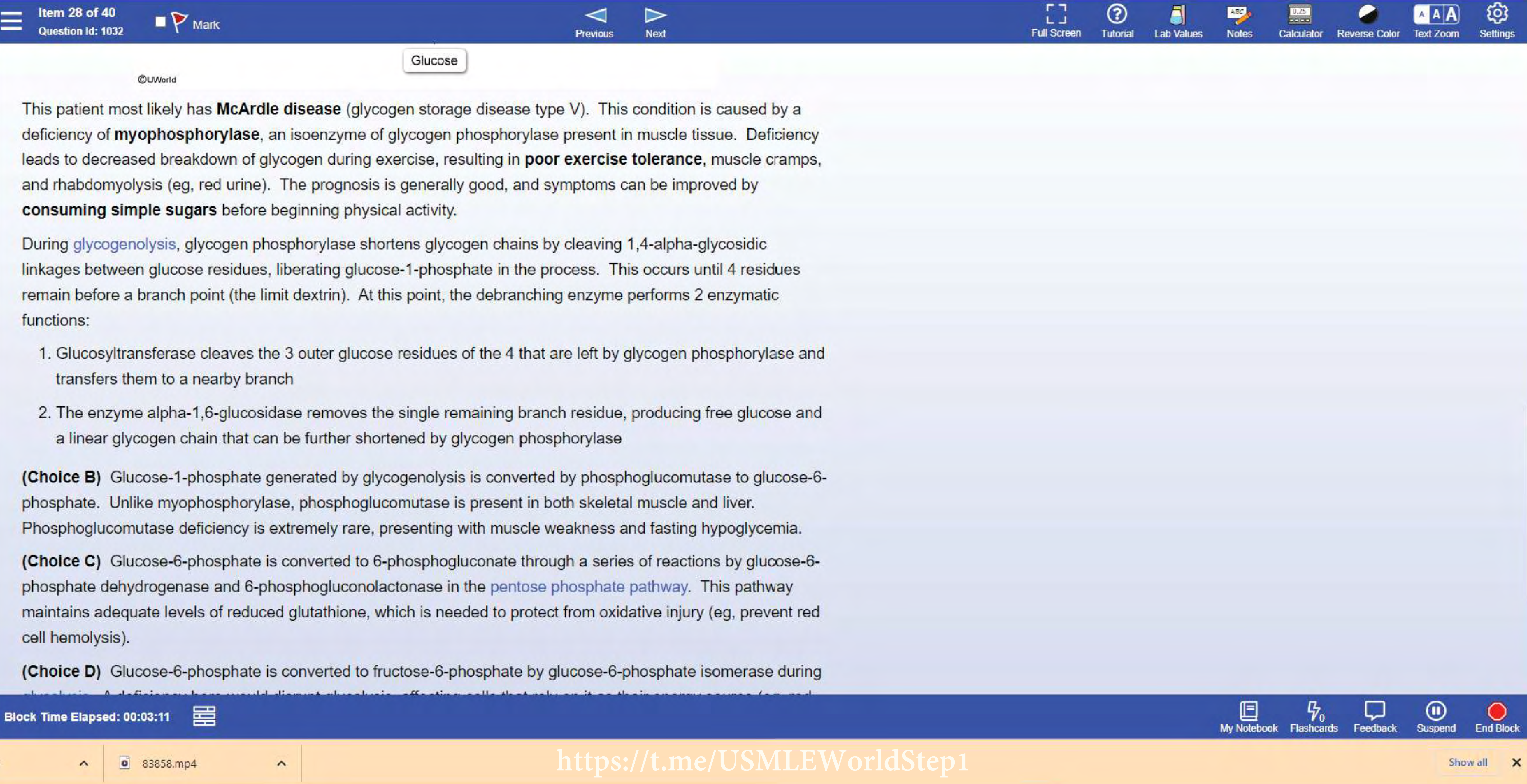
leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, muscle cramps,

and rhabdomyolysis (eg, red urine). The prognosis is generally good, and symptoms can be improved by


Item 28 of 40
Question Id: 1032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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Block Time Elapsed: 00:03:11
My Notebook
Flashcards
Feedback
Suspend
End Block
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Show all

This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by a deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, muscle cramps, and rhabdomyolysis (eg, red urine). The prognosis is generally good, and symptoms can be improved by **consuming simple sugars** before beginning physical activity.

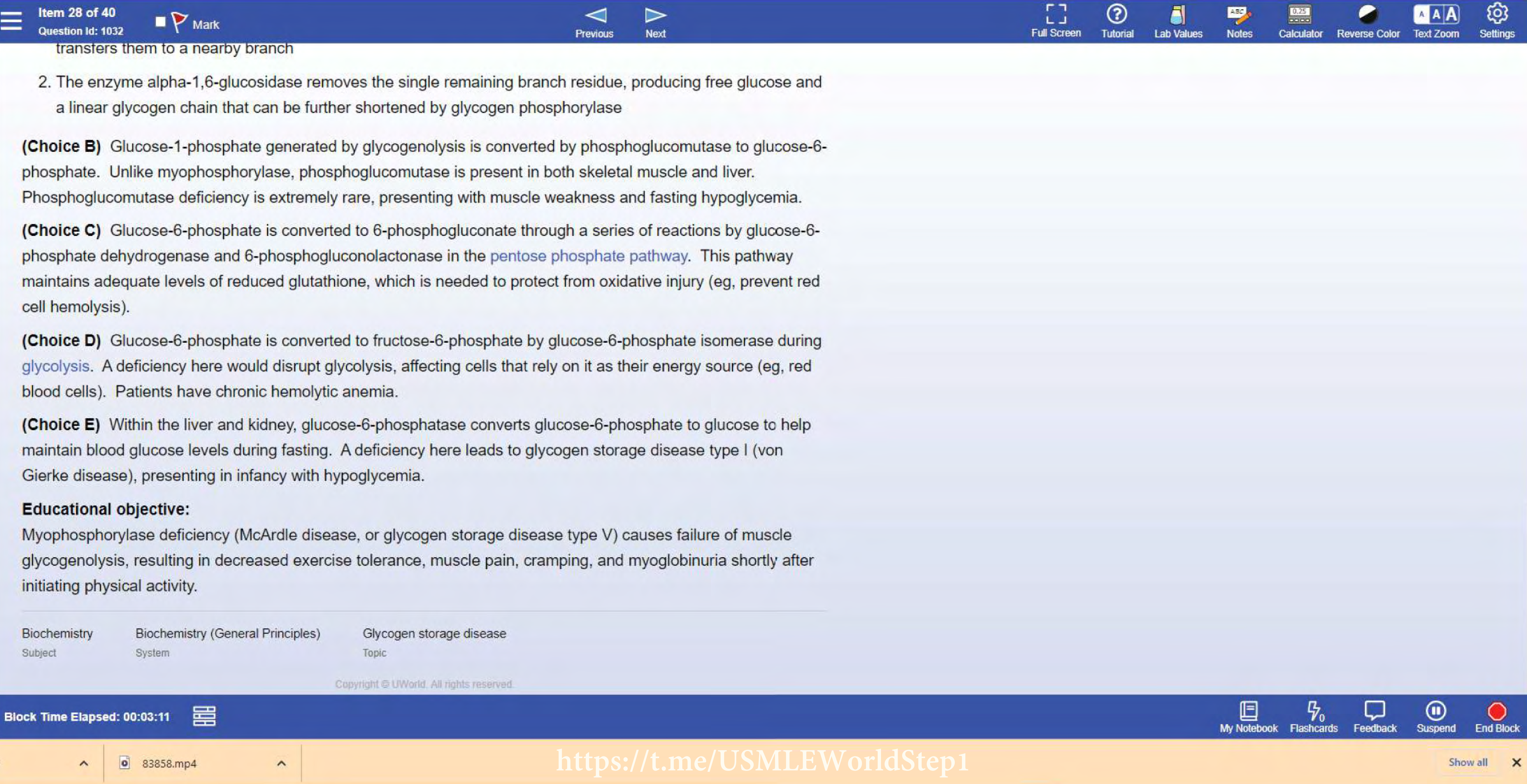
During glycogenolysis, glycogen phosphorylase shortens glycogen chains by cleaving 1,4-alpha-glycosidic linkages between glucose residues, liberating glucose-1-phosphate in the process. This occurs until 4 residues remain before a branch point (the limit dextrin). At this point, the debranching enzyme performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the 3 outer glucose residues of the 4 that are left by glycogen phosphorylase and transfers them to a nearby branch
2. The enzyme alpha-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice B) Glucose-1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose-6-phosphate. Unlike myophosphorylase, phosphoglucomutase is present in both skeletal muscle and liver. Phosphoglucomutase deficiency is extremely rare, presenting with muscle weakness and fasting hypoglycemia.

(Choice C) Glucose-6-phosphate is converted to 6-phosphogluconate through a series of reactions by glucose-6-phosphate dehydrogenase and 6-phosphogluconolactonase in the pentose phosphate pathway. This pathway maintains adequate levels of reduced glutathione, which is needed to protect from oxidative injury (eg, prevent red cell hemolysis).

(Choice D) Glucose-6-phosphate is converted to fructose-6-phosphate by glucose-6-phosphate isomerase during



Item 28 of 40
Question Id: 1032

transfers them to a nearby branch

2. The enzyme alpha-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice B) Glucose-1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose-6-phosphate. Unlike myophosphorylase, phosphoglucomutase is present in both skeletal muscle and liver. Phosphoglucomutase deficiency is extremely rare, presenting with muscle weakness and fasting hypoglycemia.

(Choice C) Glucose-6-phosphate is converted to 6-phosphogluconate through a series of reactions by glucose-6-phosphate dehydrogenase and 6-phosphogluconolactonase in the pentose phosphate pathway. This pathway maintains adequate levels of reduced glutathione, which is needed to protect from oxidative injury (eg, prevent red cell hemolysis).

(Choice D) Glucose-6-phosphate is converted to fructose-6-phosphate by glucose-6-phosphate isomerase during glycolysis. A deficiency here would disrupt glycolysis, affecting cells that rely on it as their energy source (eg, red blood cells). Patients have chronic hemolytic anemia.

(Choice E) Within the liver and kidney, glucose-6-phosphatase converts glucose-6-phosphate to glucose to help maintain blood glucose levels during fasting. A deficiency here leads to glycogen storage disease type I (von Gierke disease), presenting in infancy with hypoglycemia.

Educational objective:

Myophosphorylase deficiency (McArdle disease, or glycogen storage disease type V) causes failure of muscle glycogenolysis, resulting in decreased exercise tolerance, muscle pain, cramping, and myoglobinuria shortly after initiating physical activity.

Biochemistry	Biochemistry (General Principles)	Glycogen storage disease
Subject	System	Topic

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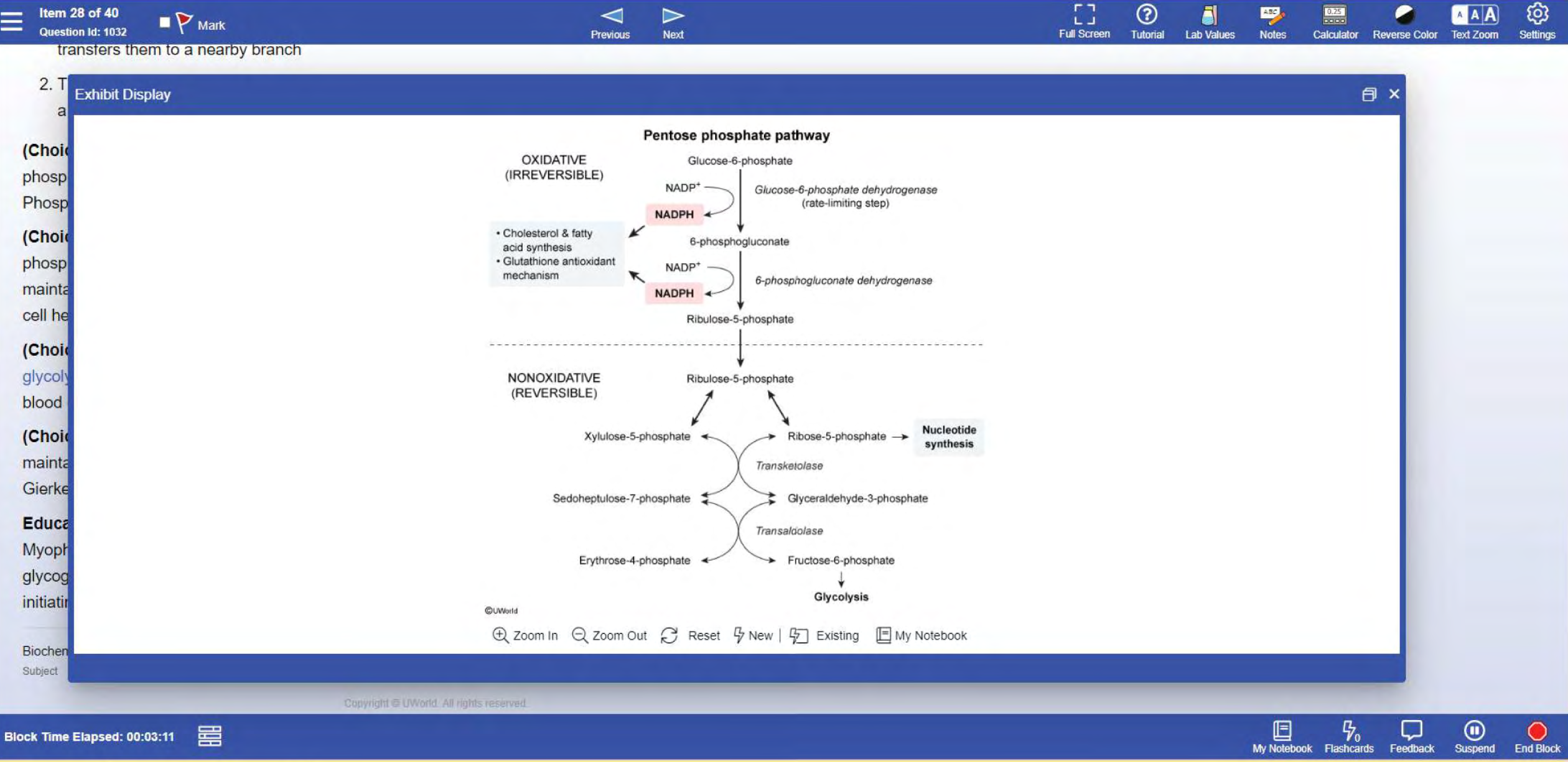
Item 28 of 40
Question Id: 1032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Exhibit Display
Pentose phosphate pathway
OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP+
NADPH
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
• Cholesterol & fatty acid synthesis
• Glutathione antioxidant mechanism
6-phosphogluconate
NADP+
NADPH
6-phosphogluconate dehydrogenase
Ribulose-5-phosphate
NONOXIDATIVE
(REVERSIBLE)
Ribulose-5-phosphate
Xylulose-5-phosphate
Ribose-5-phosphate
Nucleotide synthesis
Transketolase
Sedoheptulose-7-phosphate
Glyceraldehyde-3-phosphate
Transaldolase
Erythrose-4-phosphate
Fructose-6-phosphate
Glycolysis
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Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:03:11
My Notebook
Flashcards
Feedback
Suspend
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transfers them to a nearby branch

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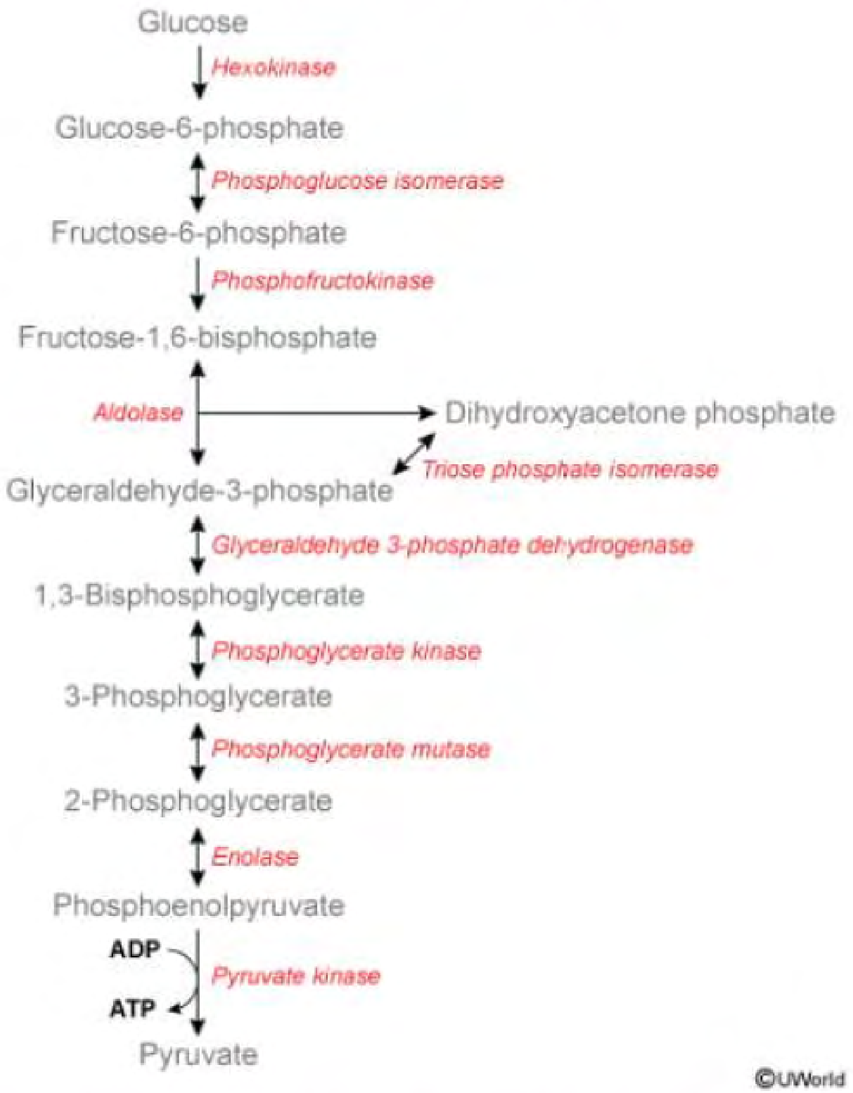
Enzymes of glycolysis


Glucose
Hexokinase
Glucose-6-phosphate
Phosphoglucose isomerase
Fructose-6-phosphate
Phosphofructokinase
Fructose-1,6-bisphosphate
Aldolase
Dihydroxyacetone phosphate
Triose phosphate isomerase
Glyceraldehyde-3-phosphate
Glyceraldehyde 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate
ADP
ATP
Pyruvate kinase
Pyruvate
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Reset
New
Existing
My Notebook

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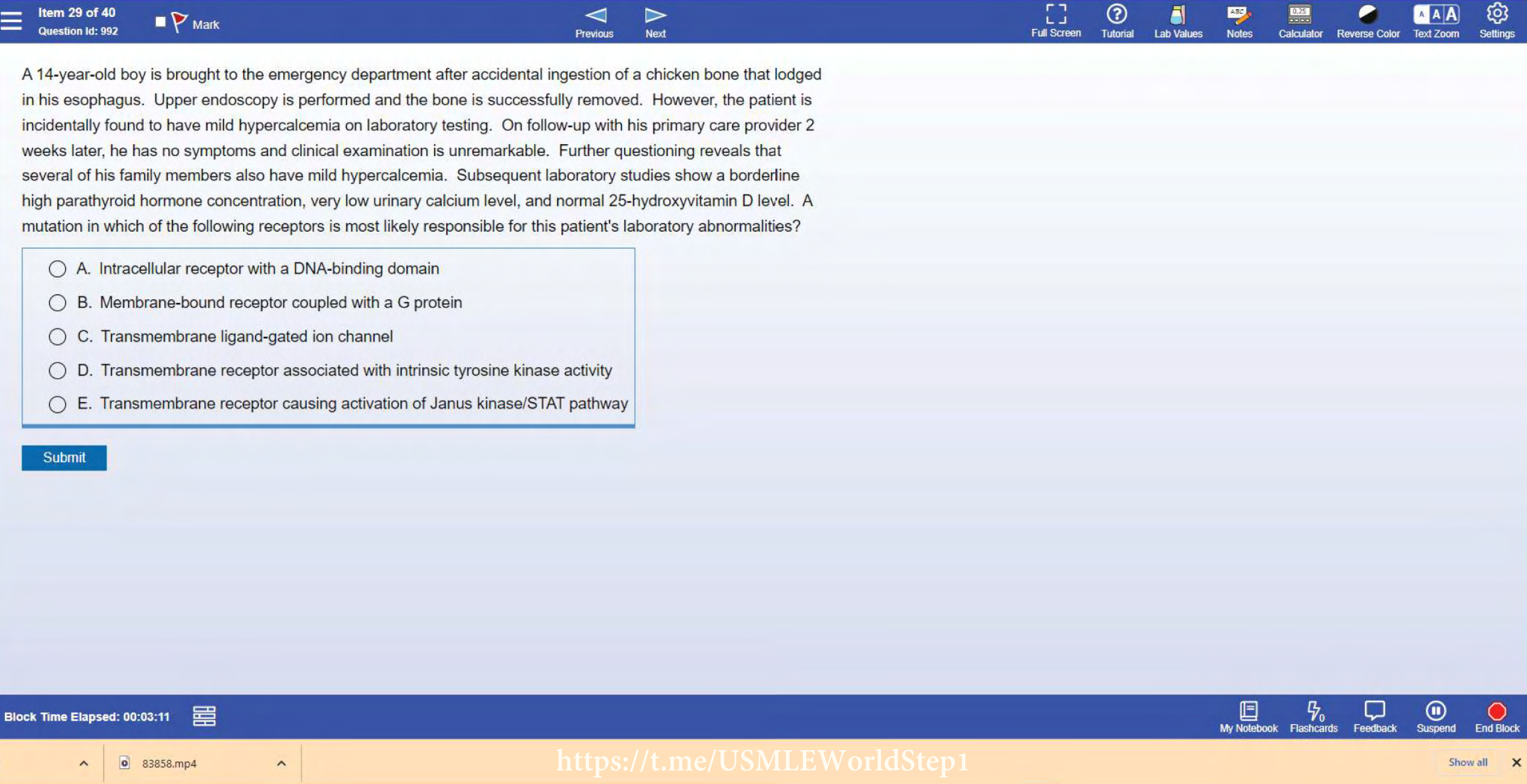
Item 29 of 40
Question Id: 992
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 14-year-old boy is brought to the emergency department after accidental ingestion of a chicken bone that lodged in his esophagus. Upper endoscopy is performed and the bone is successfully removed. However, the patient is incidentally found to have mild hypercalcemia on laboratory testing. On follow-up with his primary care provider 2 weeks later, he has no symptoms and clinical examination is unremarkable. Further questioning reveals that several of his family members also have mild hypercalcemia. Subsequent laboratory studies show a borderline high parathyroid hormone concentration, very low urinary calcium level, and normal 25-hydroxyvitamin D level. A mutation in which of the following receptors is most likely responsible for this patient's laboratory abnormalities?

○ A. Intracellular receptor with a DNA-binding domain

○ B. Membrane-bound receptor coupled with a G protein

○ C. Transmembrane ligand-gated ion channel

○ D. Transmembrane receptor associated with intrinsic tyrosine kinase activity

○ E. Transmembrane receptor causing activation of Janus kinase/STAT pathway

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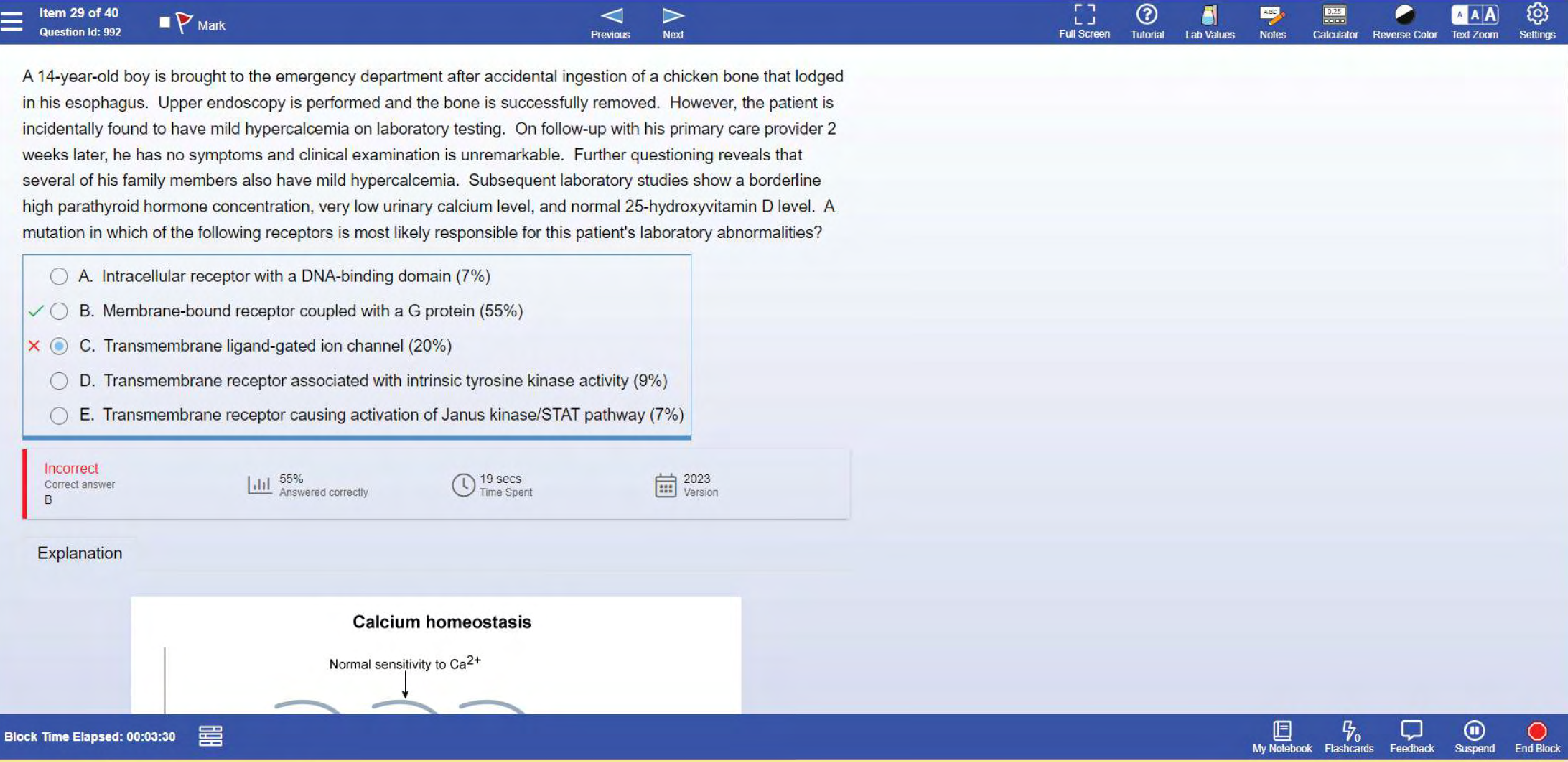
Item 29 of 40
Question Id: 992
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 14-year-old boy is brought to the emergency department after accidental ingestion of a chicken bone that lodged in his esophagus. Upper endoscopy is performed and the bone is successfully removed. However, the patient is incidentally found to have mild hypercalcemia on laboratory testing. On follow-up with his primary care provider 2 weeks later, he has no symptoms and clinical examination is unremarkable. Further questioning reveals that several of his family members also have mild hypercalcemia. Subsequent laboratory studies show a borderline high parathyroid hormone concentration, very low urinary calcium level, and normal 25-hydroxyvitamin D level. A mutation in which of the following receptors is most likely responsible for this patient's laboratory abnormalities?

- ○ A. Intracellular receptor with a DNA-binding domain (7%)
- ✓ ○ B. Membrane-bound receptor coupled with a G protein (55%)
- ✗ ● C. Transmembrane ligand-gated ion channel (20%)
- ○ D. Transmembrane receptor associated with intrinsic tyrosine kinase activity (9%)
- ○ E. Transmembrane receptor causing activation of Janus kinase/STAT pathway (7%)

Incorrect
Correct answer
B

55%
Answered correctly

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Explanation

Calcium homeostasis

Normal sensitivity to Ca^{2+}
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Feedback
Suspend
End Block

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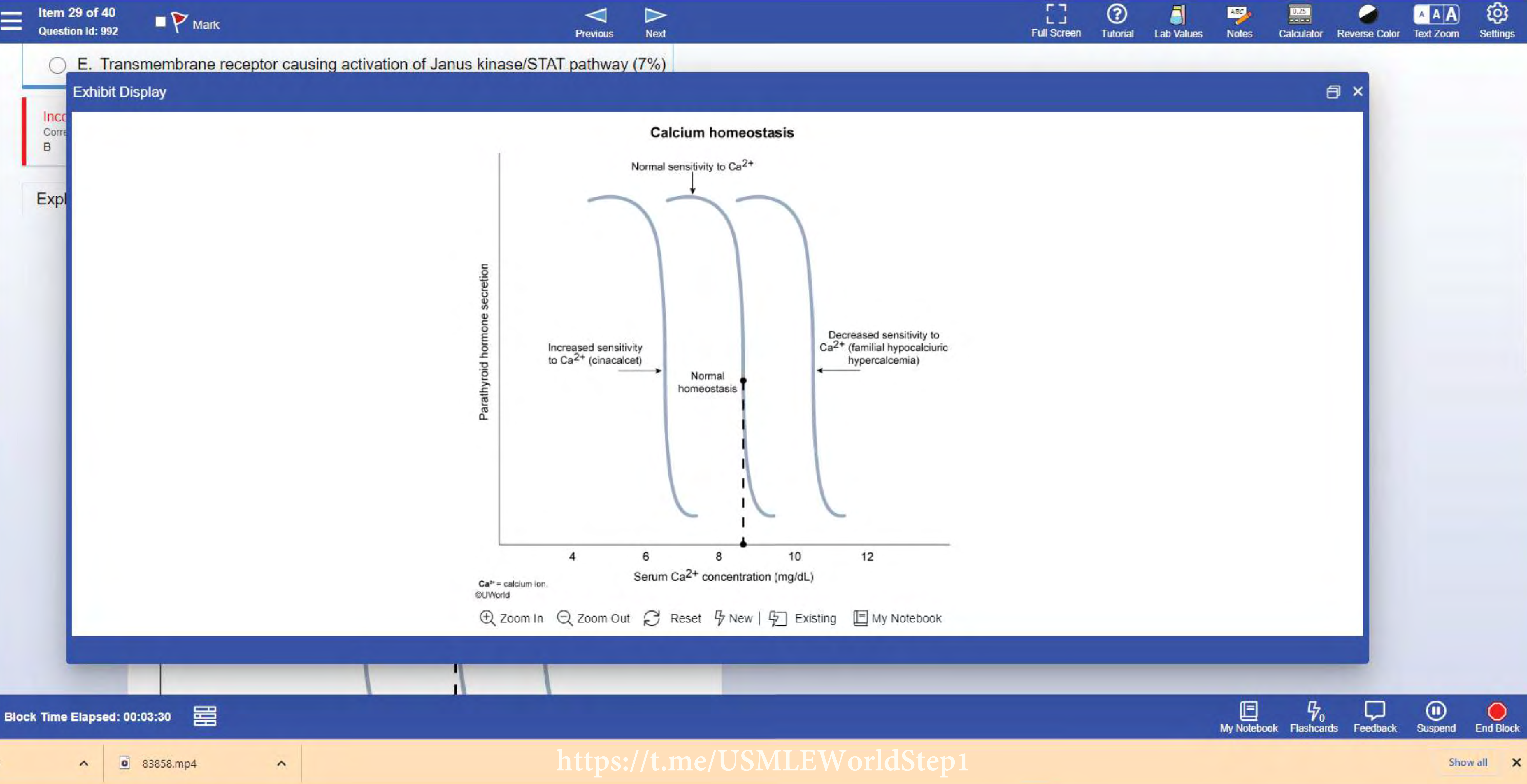

Item 29 of 40
Question Id: 992

○ E. Transmembrane receptor causing activation of Janus kinase/STAT pathway (7%)

Exhibit Display

Calcium homeostasis

Normal sensitivity to Ca2+
Increased sensitivity to Ca2+ (cinacalcet)
Normal homeostasis
Decreased sensitivity to Ca2+ (familial hypocalciuric hypercalcemia)
Parathyroid hormone secretion
4
6
8
10
12
Serum Ca2+ concentration (mg/dL)

Ca²⁺ = calcium ion.
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Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Inco
Corre
B
Expl
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
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Flashcards
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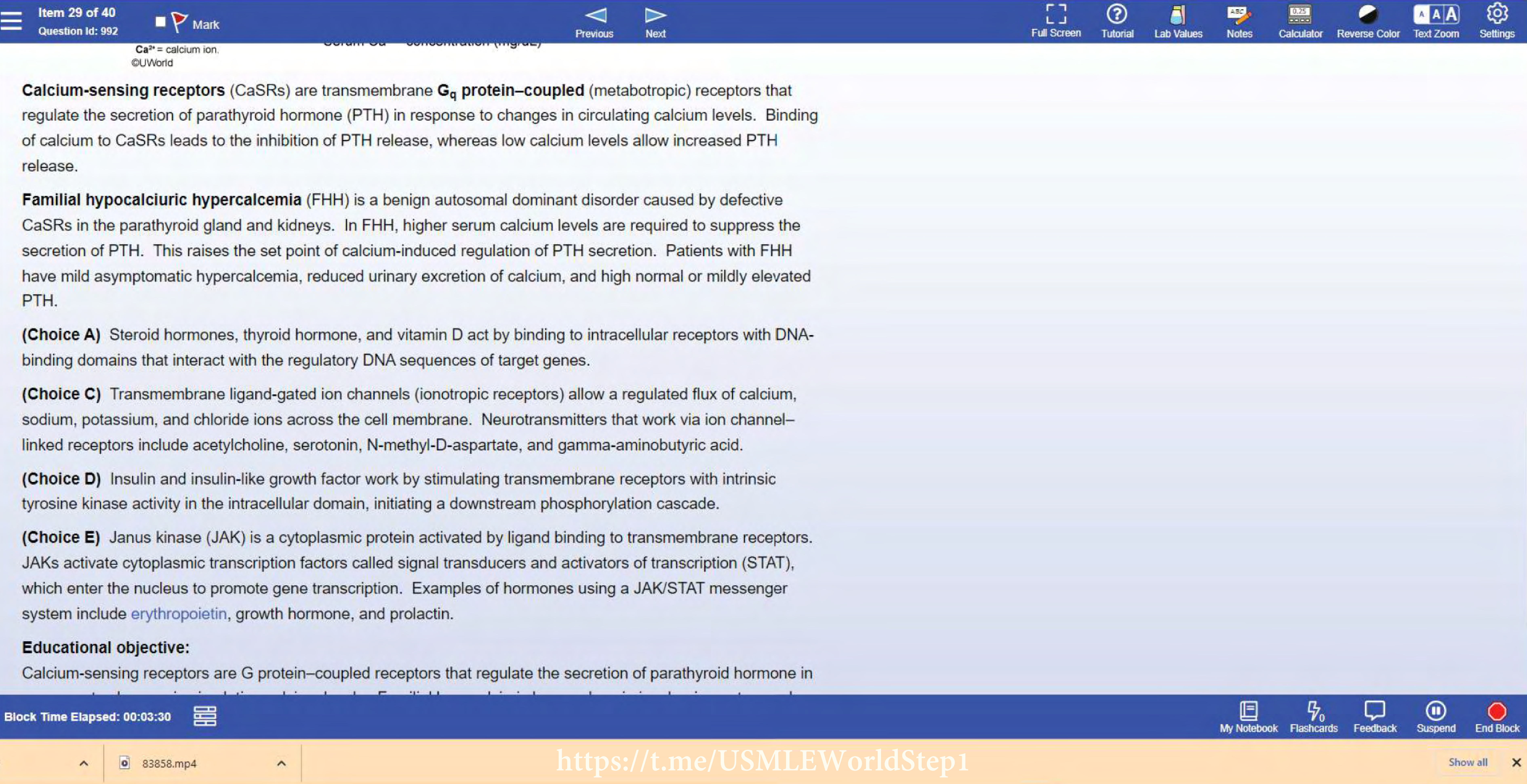

Ca^{2+} = calcium ion.
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Calcium-sensing receptors (CaSRs) are transmembrane **G$_q$ protein–coupled** (metabotropic) receptors that regulate the secretion of parathyroid hormone (PTH) in response to changes in circulating calcium levels. Binding of calcium to CaSRs leads to the inhibition of PTH release, whereas low calcium levels allow increased PTH release.

Familial hypocalciuric hypercalcemia (FHH) is a benign autosomal dominant disorder caused by defective CaSRs in the parathyroid gland and kidneys. In FHH, higher serum calcium levels are required to suppress the secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have mild asymptomatic hypercalcemia, reduced urinary excretion of calcium, and high normal or mildly elevated PTH.

(Choice A) Steroid hormones, thyroid hormone, and vitamin D act by binding to intracellular receptors with DNA-binding domains that interact with the regulatory DNA sequences of target genes.

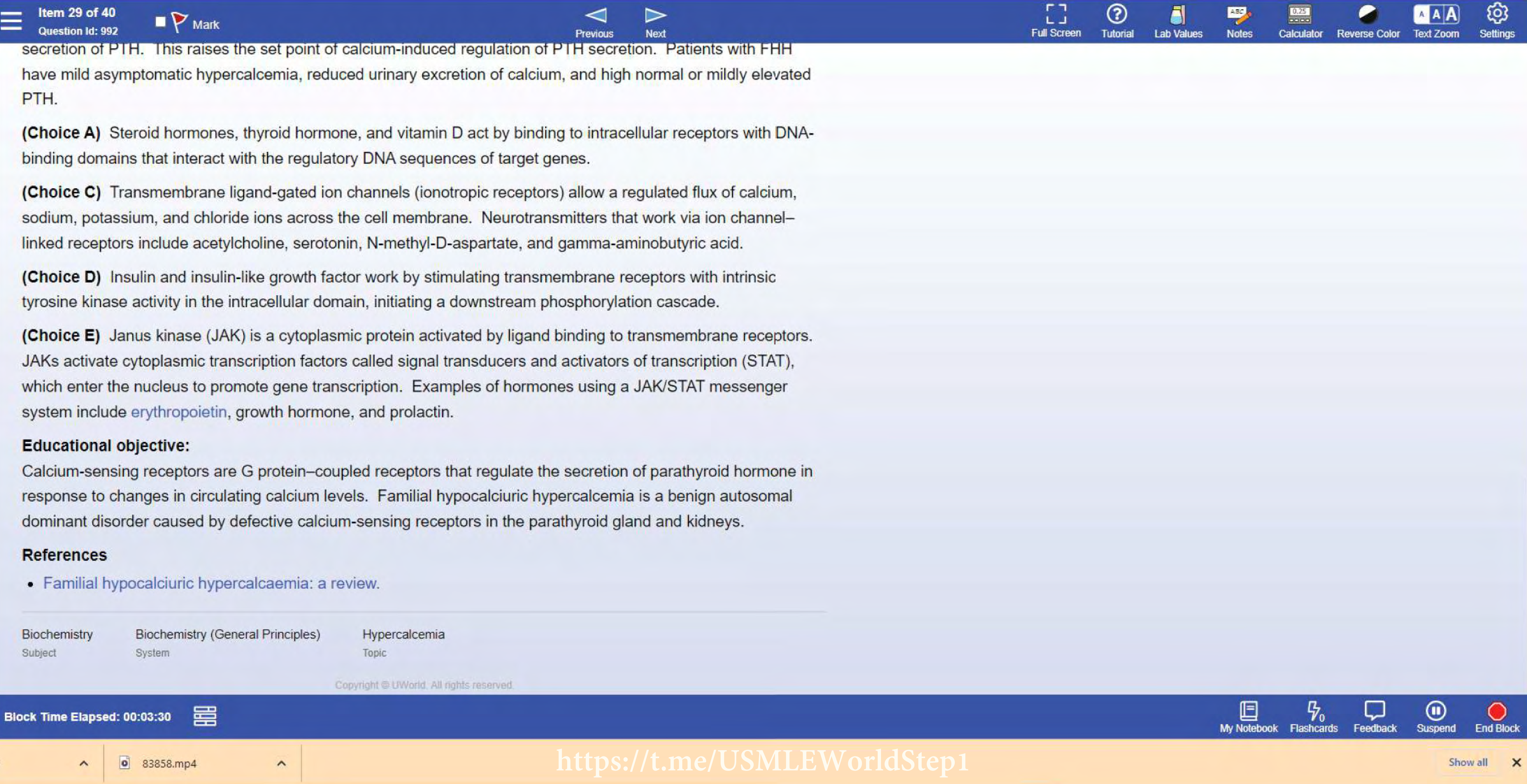
(Choice C) Transmembrane ligand-gated ion channels (ionotropic receptors) allow a regulated flux of calcium, sodium, potassium, and chloride ions across the cell membrane. Neurotransmitters that work via ion channel–linked receptors include acetylcholine, serotonin, N-methyl-D-aspartate, and gamma-aminobutyric acid.

(Choice D) Insulin and insulin-like growth factor work by stimulating transmembrane receptors with intrinsic tyrosine kinase activity in the intracellular domain, initiating a downstream phosphorylation cascade.

(Choice E) Janus kinase (JAK) is a cytoplasmic protein activated by ligand binding to transmembrane receptors. JAKs activate cytoplasmic transcription factors called signal transducers and activators of transcription (STAT), which enter the nucleus to promote gene transcription. Examples of hormones using a JAK/STAT messenger system include erythropoietin, growth hormone, and prolactin.

Educational objective:

Calcium-sensing receptors are G protein–coupled receptors that regulate the secretion of parathyroid hormone in


Item 29 of 40
Question Id: 992
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have mild asymptomatic hypercalcemia, reduced urinary excretion of calcium, and high normal or mildly elevated PTH.

(Choice A) Steroid hormones, thyroid hormone, and vitamin D act by binding to intracellular receptors with DNA-binding domains that interact with the regulatory DNA sequences of target genes.

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Educational objective:

Calcium-sensing receptors are G protein–coupled receptors that regulate the secretion of parathyroid hormone in response to changes in circulating calcium levels. Familial hypocalciuric hypercalcemia is a benign autosomal dominant disorder caused by defective calcium-sensing receptors in the parathyroid gland and kidneys.

References

- Familial hypocalciuric hypercalcaemia: a review.

Biochemistry	Biochemistry (General Principles)	Hypercalcemia
Subject	System	Topic

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Feedback
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secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have m
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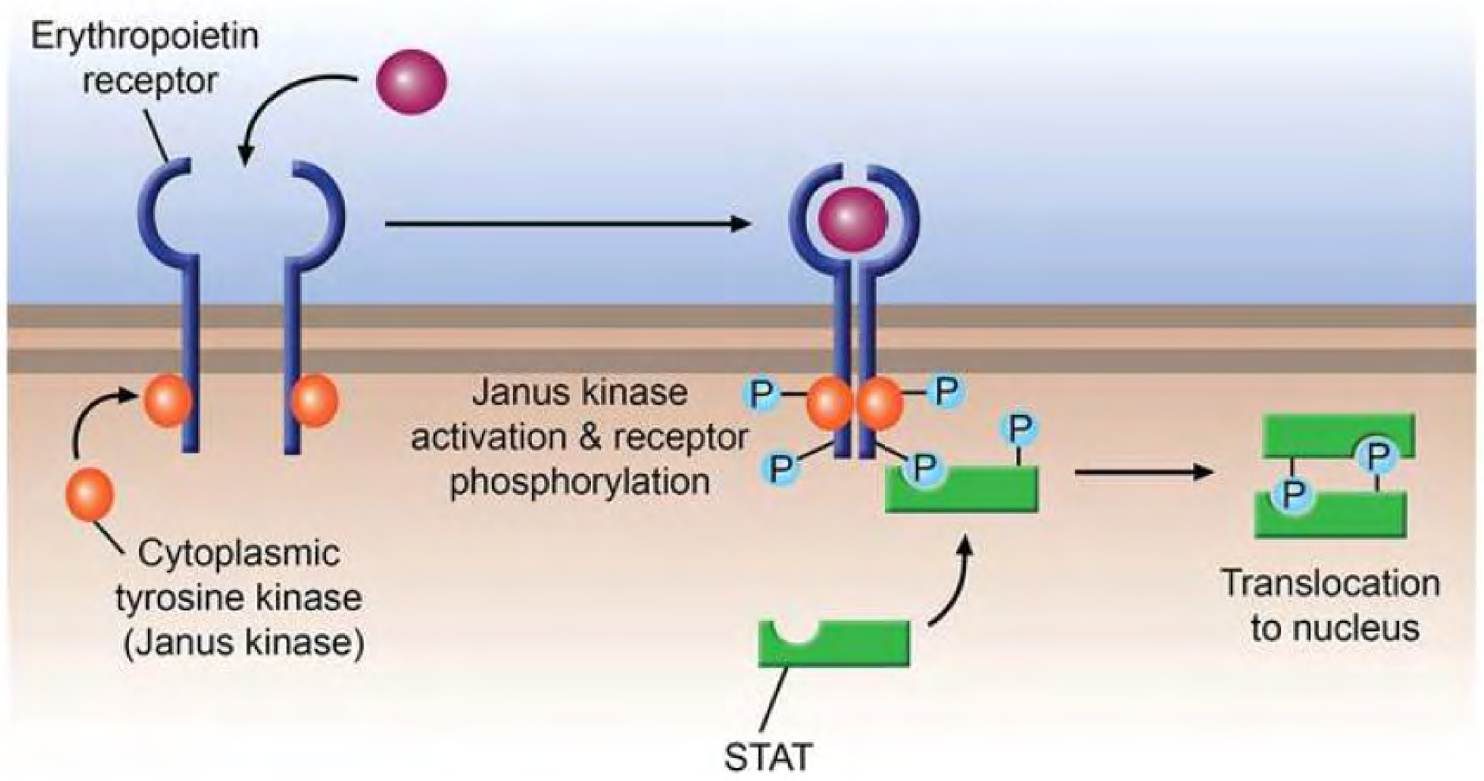
Erythropoietin signal transduction


Erythropoietin receptor
Janus kinase activation & receptor phosphorylation
P
Cytoplasmic tyrosine kinase (Janus kinase)
Translocation to nucleus
STAT

STAT = signal transducers and activators of transcription.

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Existing
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Biochem
Subject

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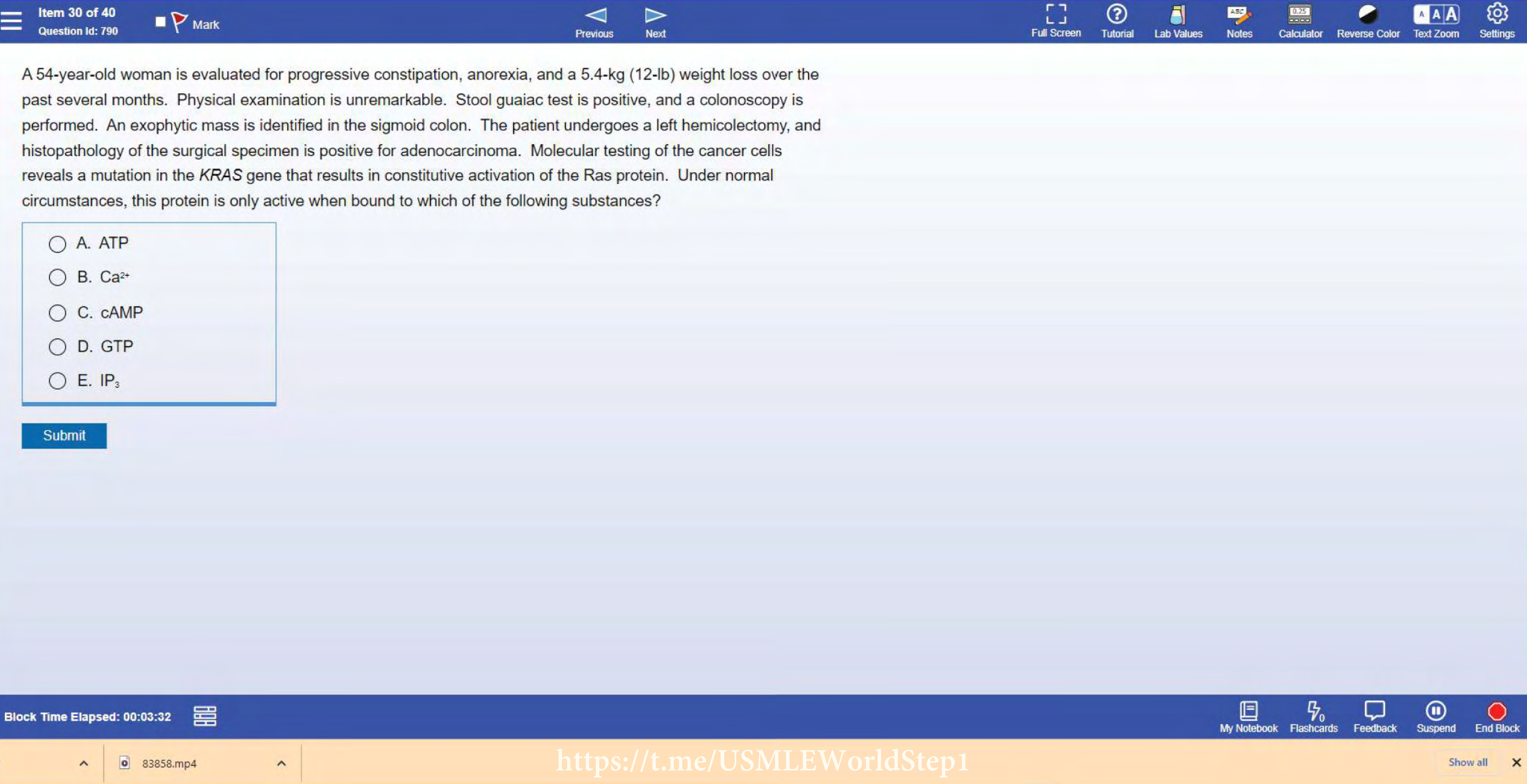
Item 30 of 40
Question Id: 790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

○ A. ATP
○ B. Ca^{2+}
○ C. cAMP
○ D. GTP
○ E. IP_3

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Flashcards
Feedback
Suspend
End Block
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A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

○ A. ATP (13%)
✗ ● B. Ca^{2+} (7%)
○ C. cAMP (15%)
✓ ○ D. GTP (55%)
○ E. IP_3 (8%)

Incorrect
Correct answer
D

55%
Answered correctly

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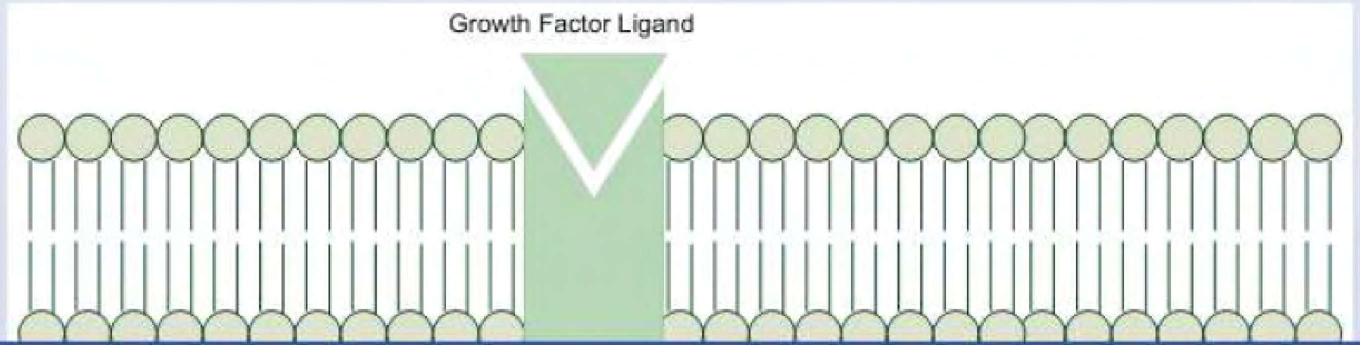
2023
Version

Explanation



83858.mp4
Show all

Item 30 of 40
Question Id: 790

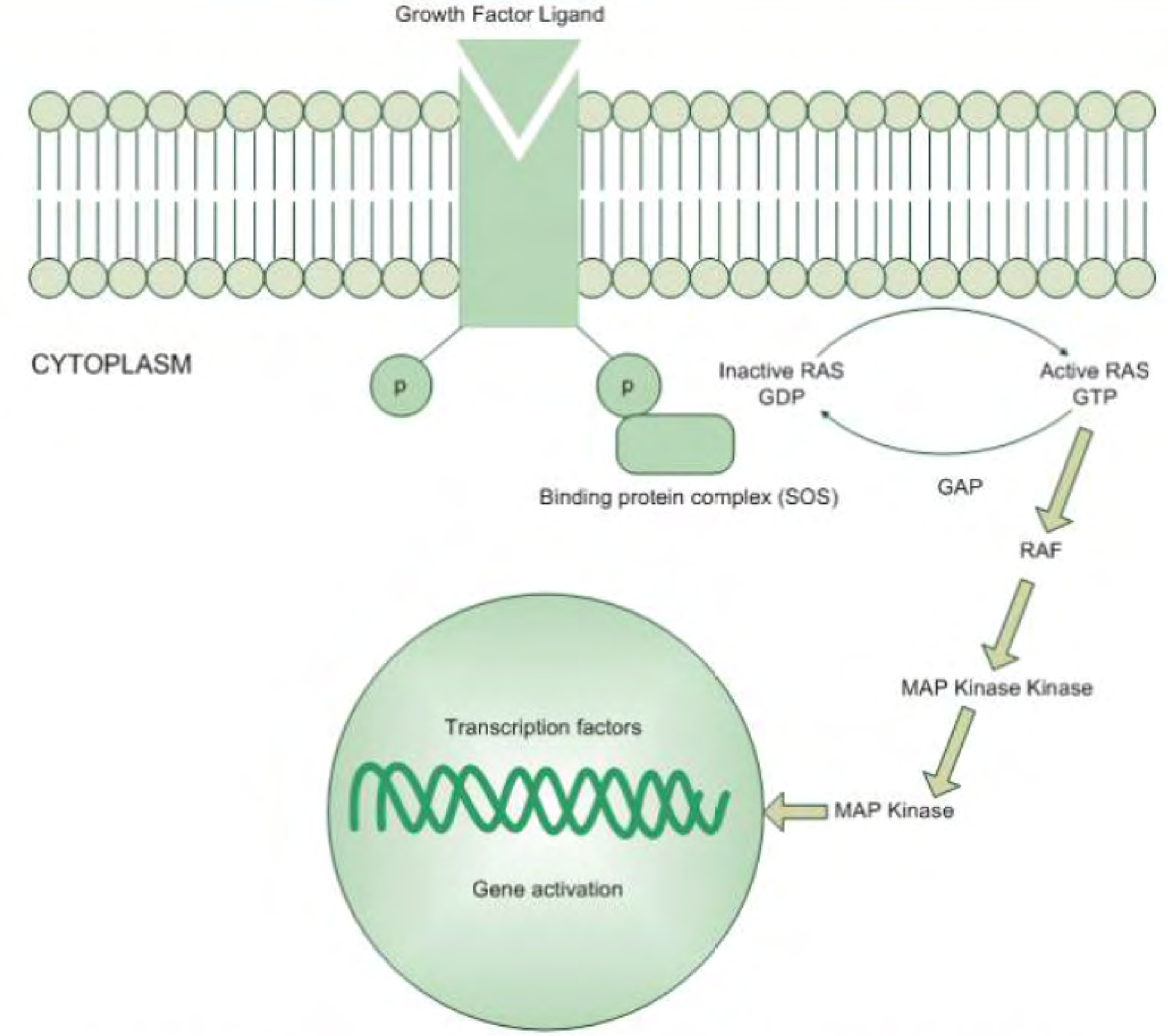
☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Growth Factor Ligand

Exhibit Display


Growth Factor Ligand
CYTOPLASM
p
p
Inactive RAS
GDP
Active RAS
GTP
GAP
Binding protein complex (SOS)
RAF
MAP Kinase Kinase
MAP Kinase
Transcription factors
Gene activation

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GDP removal and GTP binding. Activated Ras then begins a phosphorylation cascade that results in the activation of **mitogen-activated protein kinase (MAPK)**, which enters the nucleus to influence gene transcription.

Block Time Elapsed: 00:03:34

My Notebook Flashcards Feedback Suspend End Block

83858.mp4

Show all

Item 30 of 40
Question Id: 790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states: an **inactive GDP-bound state** and an **active GTP-bound state**. Ras becomes activated when a growth factor ligand binds to a **receptor tyrosine kinase** located on the cell membrane, causing autophosphorylation of the receptor. This triggers binding of adaptor proteins that interact with Ras, promoting GDP removal and GTP binding. Activated Ras then begins a phosphorylation cascade that results in the activation of **mitogen-activated protein kinase (MAPK)**, which enters the nucleus to influence gene transcription.

Ras proteins have intrinsic GTPase activity that allows them to hydrolyze GTP; this mechanism prevents accumulation of active Ras (GTP-bound) in the absence of hormonal signaling. *RAS* gene mutations can lead to decreased intrinsic GTPase activity; this results in a constitutively activated Ras protein that causes constant and unregulated cell proliferation. *RAS* mutations are commonly identified in cancerous tumors, specifically colorectal and pancreatic malignancies.

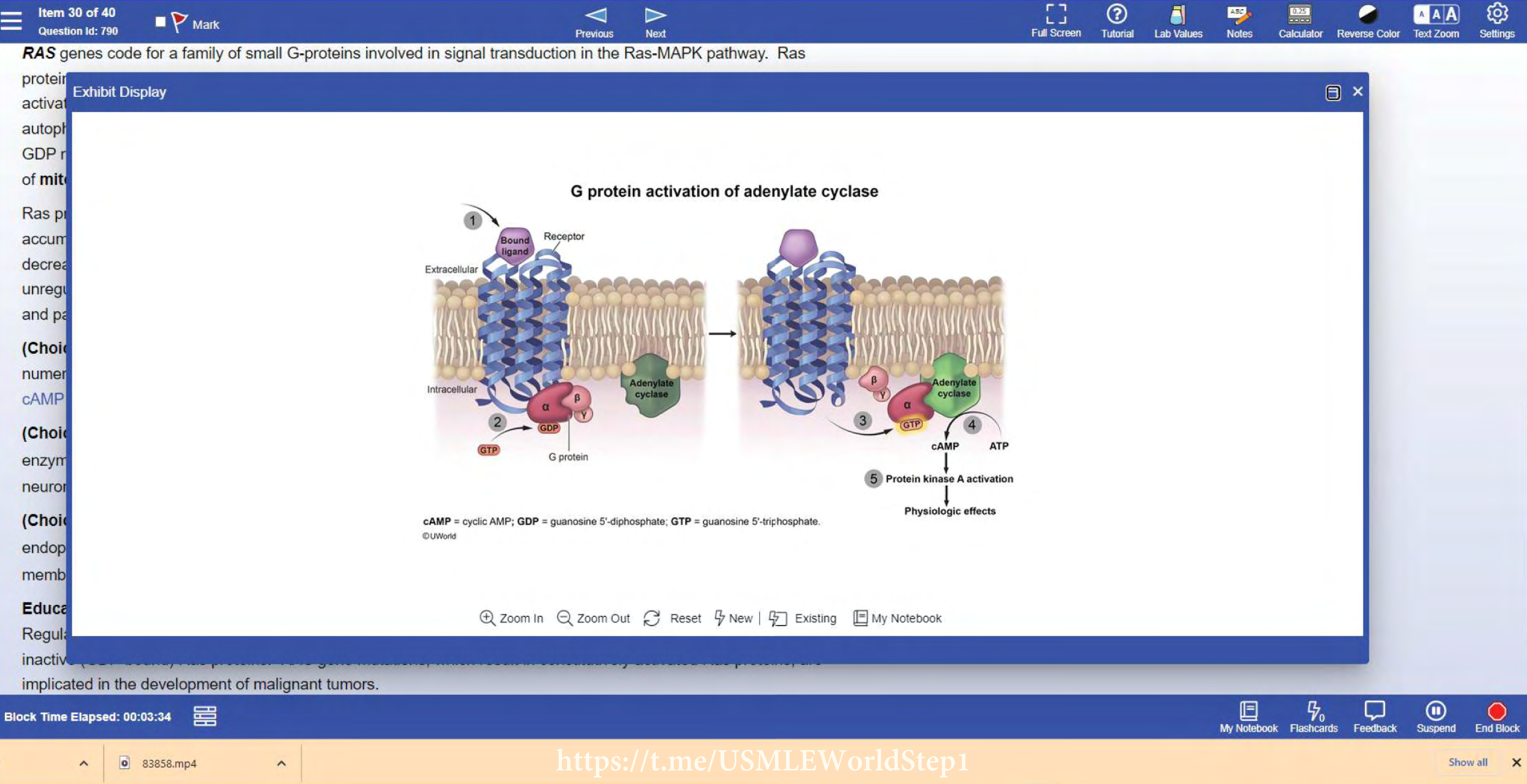
(Choices A and C) ATP serves as a phosphate source for kinase-dependent phosphorylation reactions involved in numerous intracellular signaling pathways. It is also used as a substrate to produce cyclic AMP (cAMP) in the cAMP second messenger system.

(Choice B) Ca^{2+} is important for cell signaling as its intracellular presence alters the function of many proteins and enzymes. Ca^{2+} is required for many basic physiologic activities including apoptosis, muscular contraction, and neuronal transmission.

(Choice E) IP_3 is the water-soluble component of the IP_3/DAG second messenger system. IP_3 acts on the endoplasmic reticulum to cause intracellular Ca^{2+} release while DAG remains in the cell membrane and activates membrane-bound protein kinases.

Educational objective:

Regulation of the Ras-MAPK signal transduction pathway requires a balance between active (GTP-bound) and inactive (GDP-bound) Ras proteins. *RAS* gene mutations, which result in constitutively activated Ras proteins, are implicated in the development of malignant tumors.


Item 30 of 40
Question Id: 790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras

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implicated in the development of malignant tumors.

Exhibit Display

G protein activation of adenylate cyclase

1
Bound ligand
Receptor
Extracellular
Intracellular
Adenylate cyclase
α
β
γ
2
GDP
GTP
G protein
3
GTP
4
cAMP
ATP
5
Protein kinase A activation
Physiologic effects

cAMP = cyclic AMP; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate.

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Reset
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Existing
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Flashcards
Feedback
Suspend
End Block
83858.mp4
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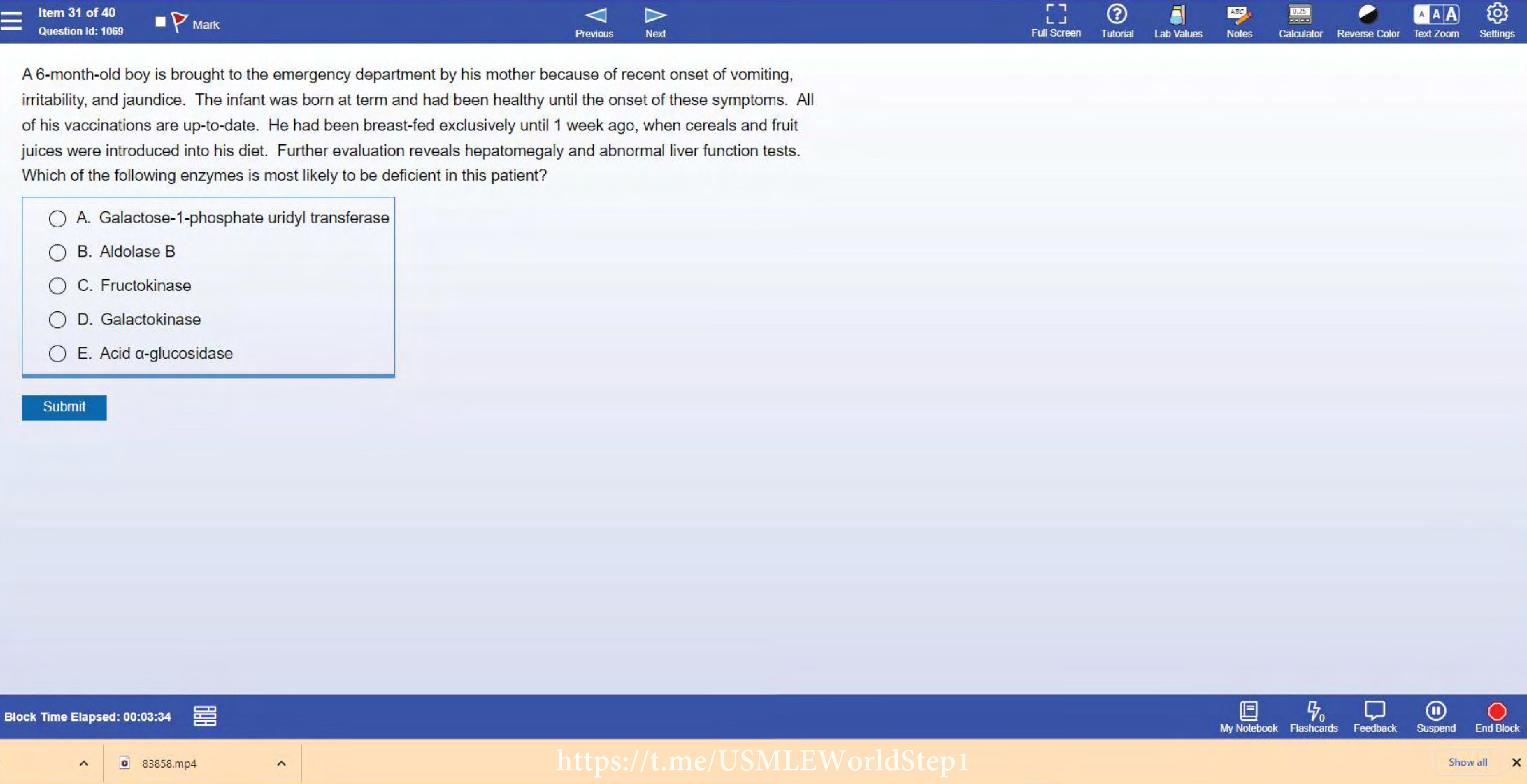
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Mark
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Item 31 of 40
Question Id: 1069

A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

- ○ A. Galactose-1-phosphate uridyl transferase
- ○ B. Aldolase B
- ○ C. Fructokinase
- ○ D. Galactokinase
- ○ E. Acid α-glucosidase

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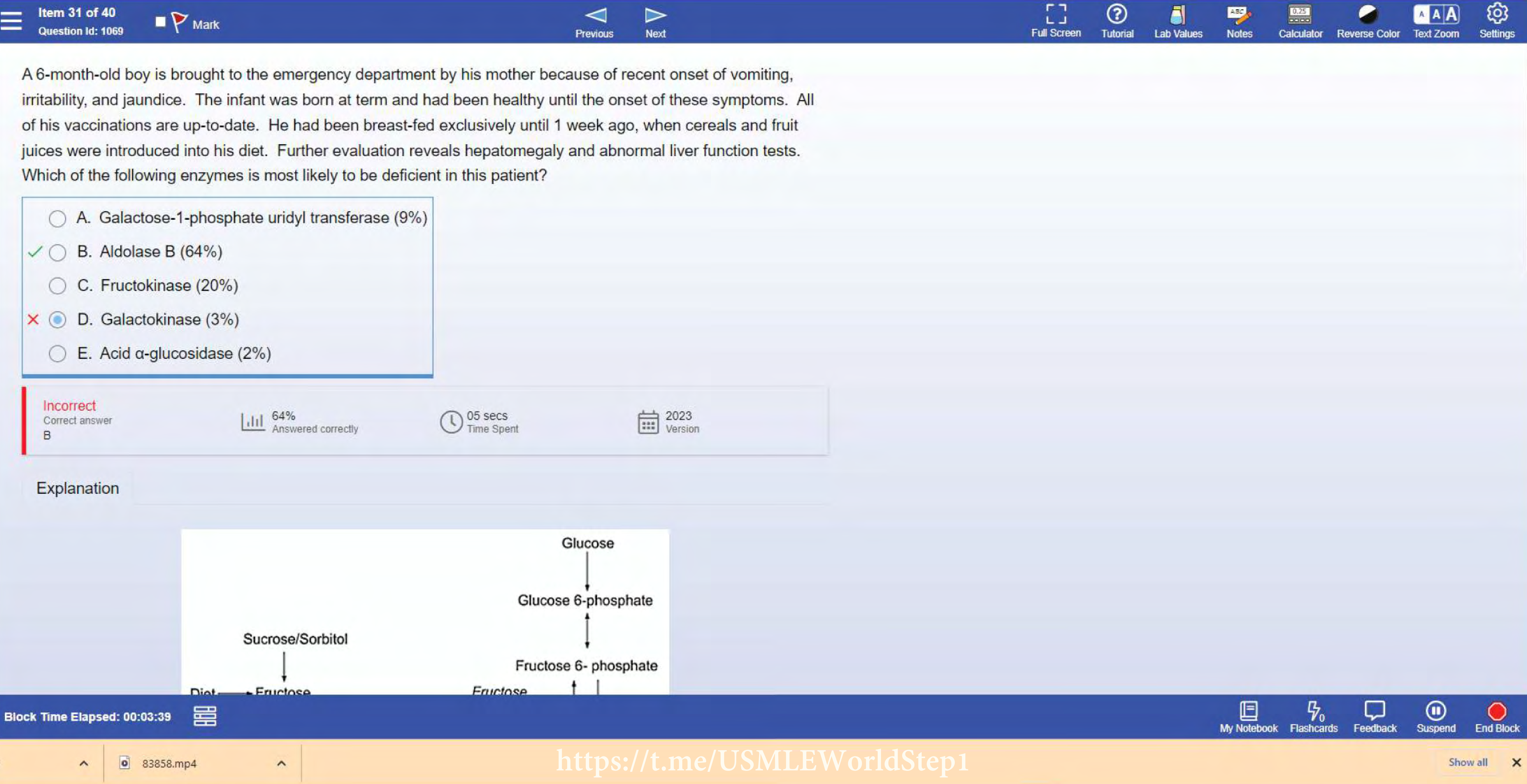

Item 31 of 40
Question Id: 1069
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

○ A. Galactose-1-phosphate uridyl transferase (9%)

✓ ○ B. Aldolase B (64%)

○ C. Fructokinase (20%)

✗ ● D. Galactokinase (3%)

○ E. Acid α-glucosidase (2%)

Incorrect
Correct answer
B

64%
Answered correctly

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2023
Version

Explanation

Glucose
Glucose 6-phosphate
Sucrose/Sorbitol
Fructose 6- phosphate
Diet
Fructose
Fructose

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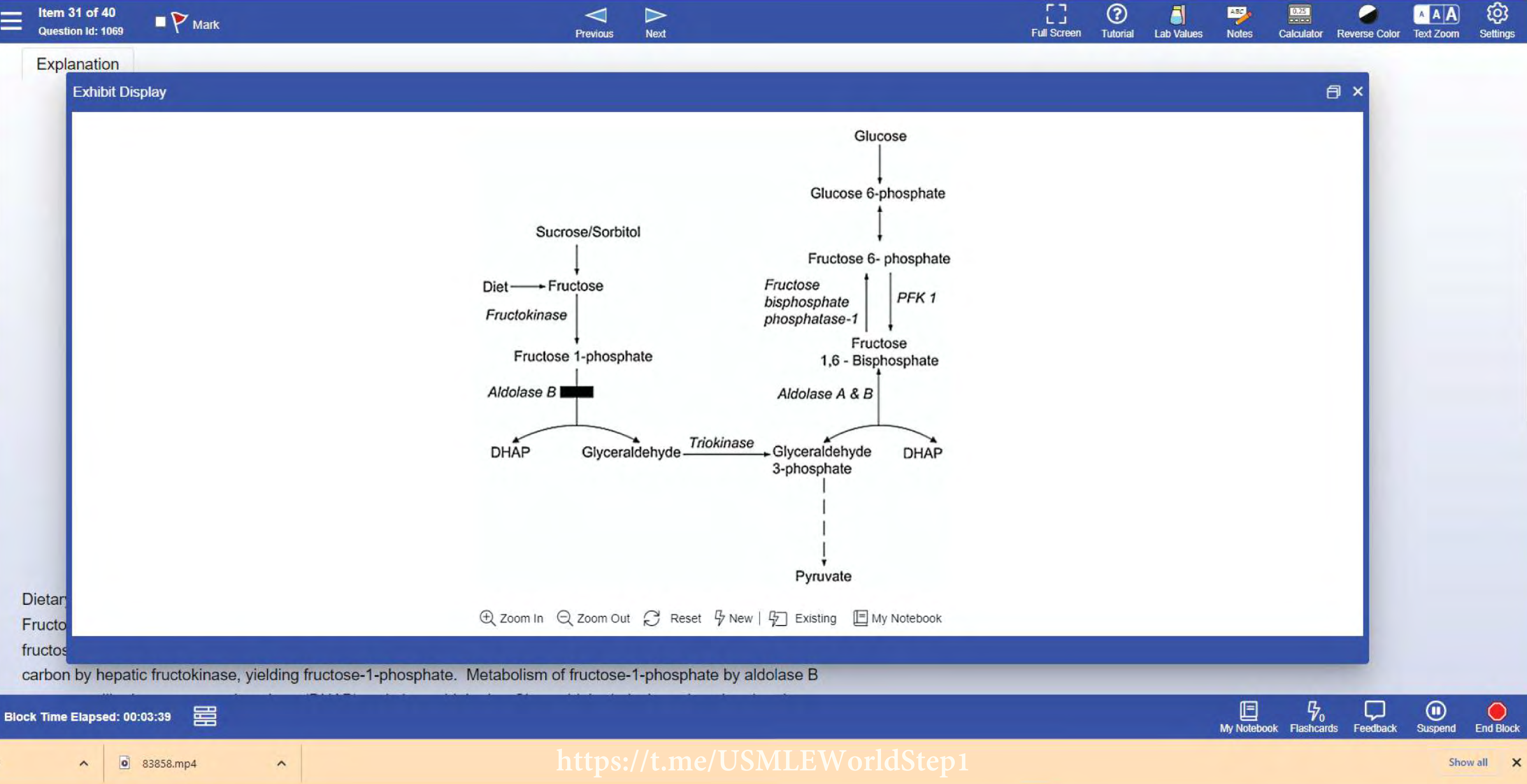
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all


Item 31 of 40
Question Id: 1069
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Glucose
Glucose 6-phosphate
Fructose 6- phosphate
Fructose bisphosphate phosphatase-1
PFK 1
Fructose 1,6 - Bisphosphate
Aldolase A & B
Sucrose/Sorbitol
Diet
Fructose
Fructokinase
Fructose 1-phosphate
Aldolase B
DHAP
Glyceraldehyde
Triokinase
Glyceraldehyde 3-phosphate
DHAP
Pyruvate
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:03:39
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Dietar

Fructo

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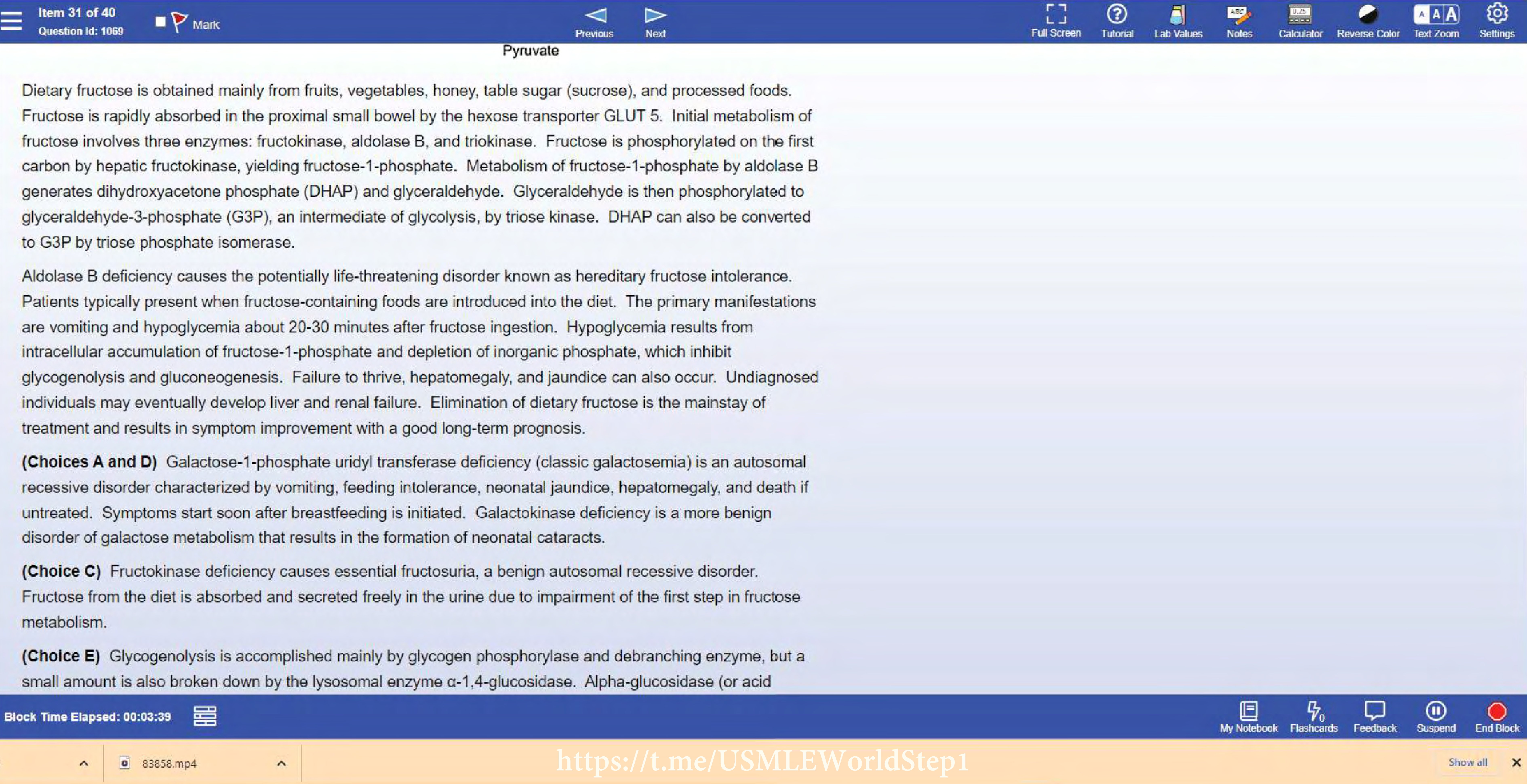
carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B



Pyruvate

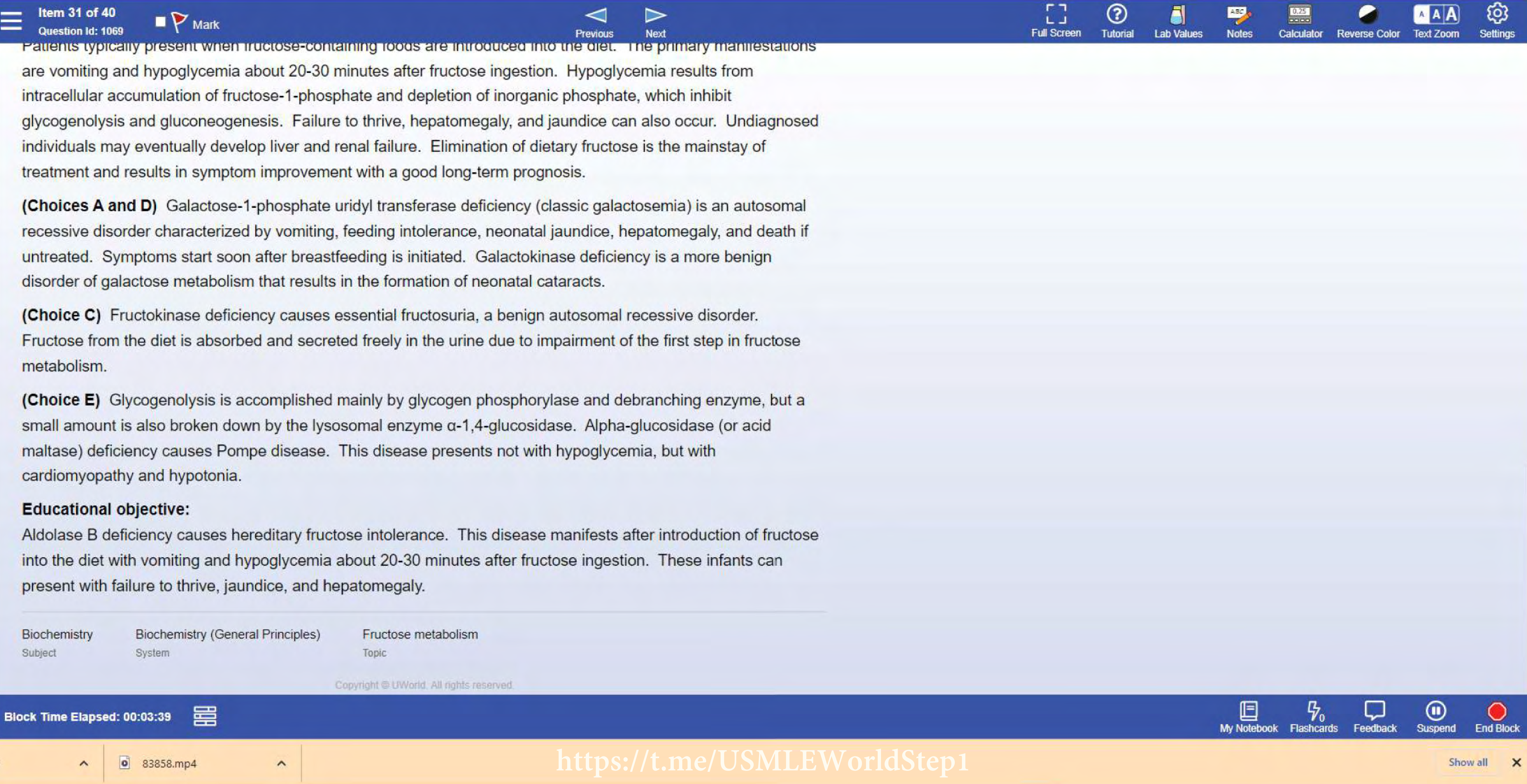
Dietary fructose is obtained mainly from fruits, vegetables, honey, table sugar (sucrose), and processed foods. Fructose is rapidly absorbed in the proximal small bowel by the hexose transporter GLUT 5. Initial metabolism of fructose involves three enzymes: fructokinase, aldolase B, and triokinase. Fructose is phosphorylated on the first carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is then phosphorylated to glyceraldehyde-3-phosphate (G3P), an intermediate of glycolysis, by triose kinase. DHAP can also be converted to G3P by triose phosphate isomerase.

Aldolase B deficiency causes the potentially life-threatening disorder known as hereditary fructose intolerance. Patients typically present when fructose-containing foods are introduced into the diet. The primary manifestations are vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. Hypoglycemia results from intracellular accumulation of fructose-1-phosphate and depletion of inorganic phosphate, which inhibit glycogenolysis and gluconeogenesis. Failure to thrive, hepatomegaly, and jaundice can also occur. Undiagnosed individuals may eventually develop liver and renal failure. Elimination of dietary fructose is the mainstay of treatment and results in symptom improvement with a good long-term prognosis.

(Choices A and D) Galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) is an autosomal recessive disorder characterized by vomiting, feeding intolerance, neonatal jaundice, hepatomegaly, and death if untreated. Symptoms start soon after breastfeeding is initiated. Galactokinase deficiency is a more benign disorder of galactose metabolism that results in the formation of neonatal cataracts.

(Choice C) Fructokinase deficiency causes essential fructosuria, a benign autosomal recessive disorder. Fructose from the diet is absorbed and secreted freely in the urine due to impairment of the first step in fructose metabolism.

(Choice E) Glycogenolysis is accomplished mainly by glycogen phosphorylase and debranching enzyme, but a small amount is also broken down by the lysosomal enzyme α-1,4-glucosidase. Alpha-glucosidase (or acid



Patients typically present when fructose-containing foods are introduced into the diet. The primary manifestations are vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. Hypoglycemia results from intracellular accumulation of fructose-1-phosphate and depletion of inorganic phosphate, which inhibit glycogenolysis and gluconeogenesis. Failure to thrive, hepatomegaly, and jaundice can also occur. Undiagnosed individuals may eventually develop liver and renal failure. Elimination of dietary fructose is the mainstay of treatment and results in symptom improvement with a good long-term prognosis.

(Choices A and D) Galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) is an autosomal recessive disorder characterized by vomiting, feeding intolerance, neonatal jaundice, hepatomegaly, and death if untreated. Symptoms start soon after breastfeeding is initiated. Galactokinase deficiency is a more benign disorder of galactose metabolism that results in the formation of neonatal cataracts.

(Choice C) Fructokinase deficiency causes essential fructosuria, a benign autosomal recessive disorder. Fructose from the diet is absorbed and secreted freely in the urine due to impairment of the first step in fructose metabolism.

(Choice E) Glycogenolysis is accomplished mainly by glycogen phosphorylase and debranching enzyme, but a small amount is also broken down by the lysosomal enzyme α-1,4-glucosidase. Alpha-glucosidase (or acid maltase) deficiency causes Pompe disease. This disease presents not with hypoglycemia, but with cardiomyopathy and hypotonia.

Educational objective:

Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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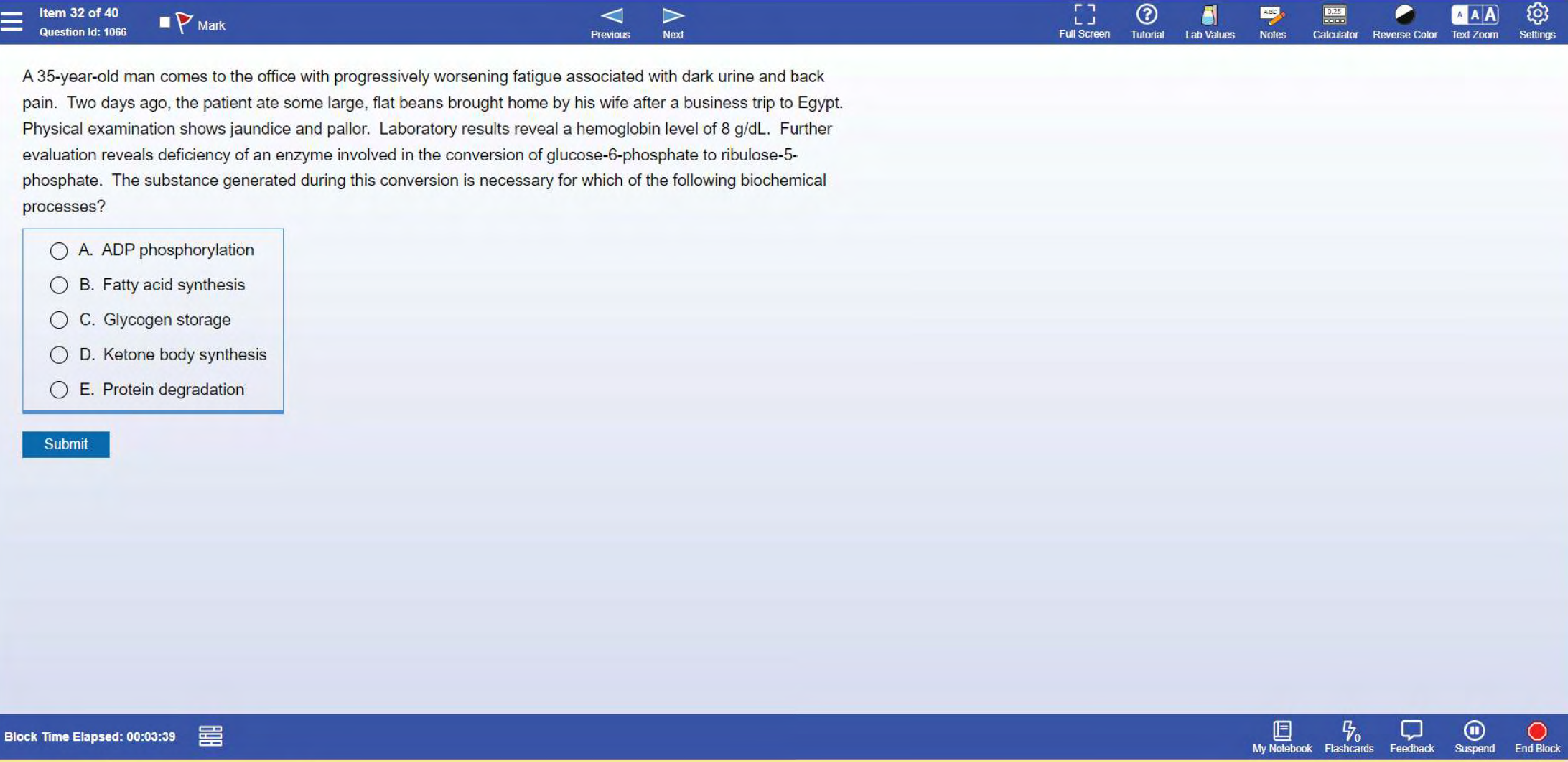
Item 32 of 40
Question Id: 1066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 35-year-old man comes to the office with progressively worsening fatigue associated with dark urine and back pain. Two days ago, the patient ate some large, flat beans brought home by his wife after a business trip to Egypt. Physical examination shows jaundice and pallor. Laboratory results reveal a hemoglobin level of 8 g/dL. Further evaluation reveals deficiency of an enzyme involved in the conversion of glucose-6-phosphate to ribulose-5-phosphate. The substance generated during this conversion is necessary for which of the following biochemical processes?

○ A. ADP phosphorylation
○ B. Fatty acid synthesis
○ C. Glycogen storage
○ D. Ketone body synthesis
○ E. Protein degradation

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My Notebook
Flashcards
Feedback
Suspend
End Block

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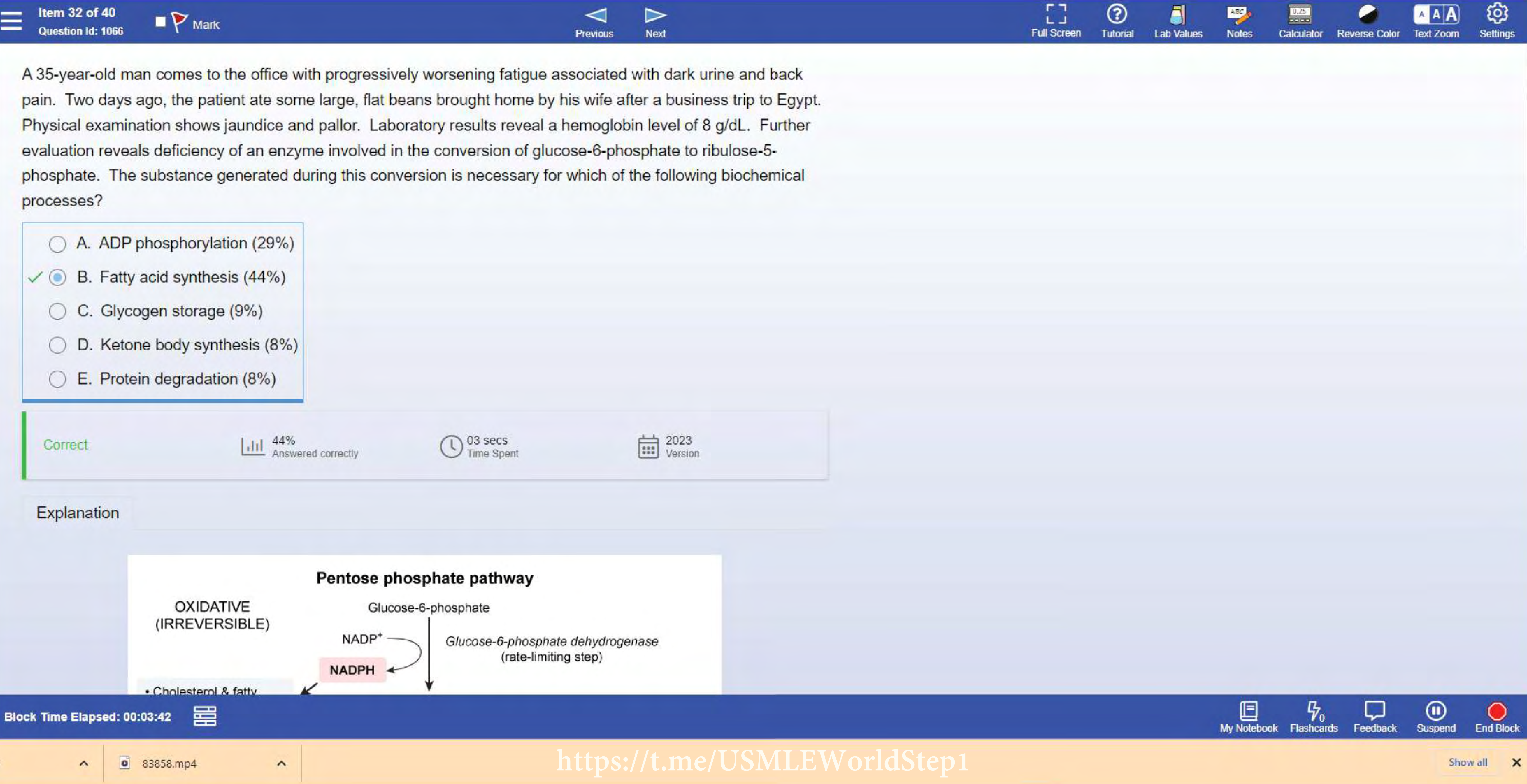
Show all


Item 32 of 40
Question Id: 1066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. ADP phosphorylation (29%)

✓ ● B. Fatty acid synthesis (44%)

○ C. Glycogen storage (9%)

○ D. Ketone body synthesis (8%)

○ E. Protein degradation (8%)

Correct

44% Answered correctly

03 secs Time Spent

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Explanation

Pentose phosphate pathway
OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP+
NADPH
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
• Cholesterol & fatty
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My Notebook
Flashcards
Feedback
Suspend
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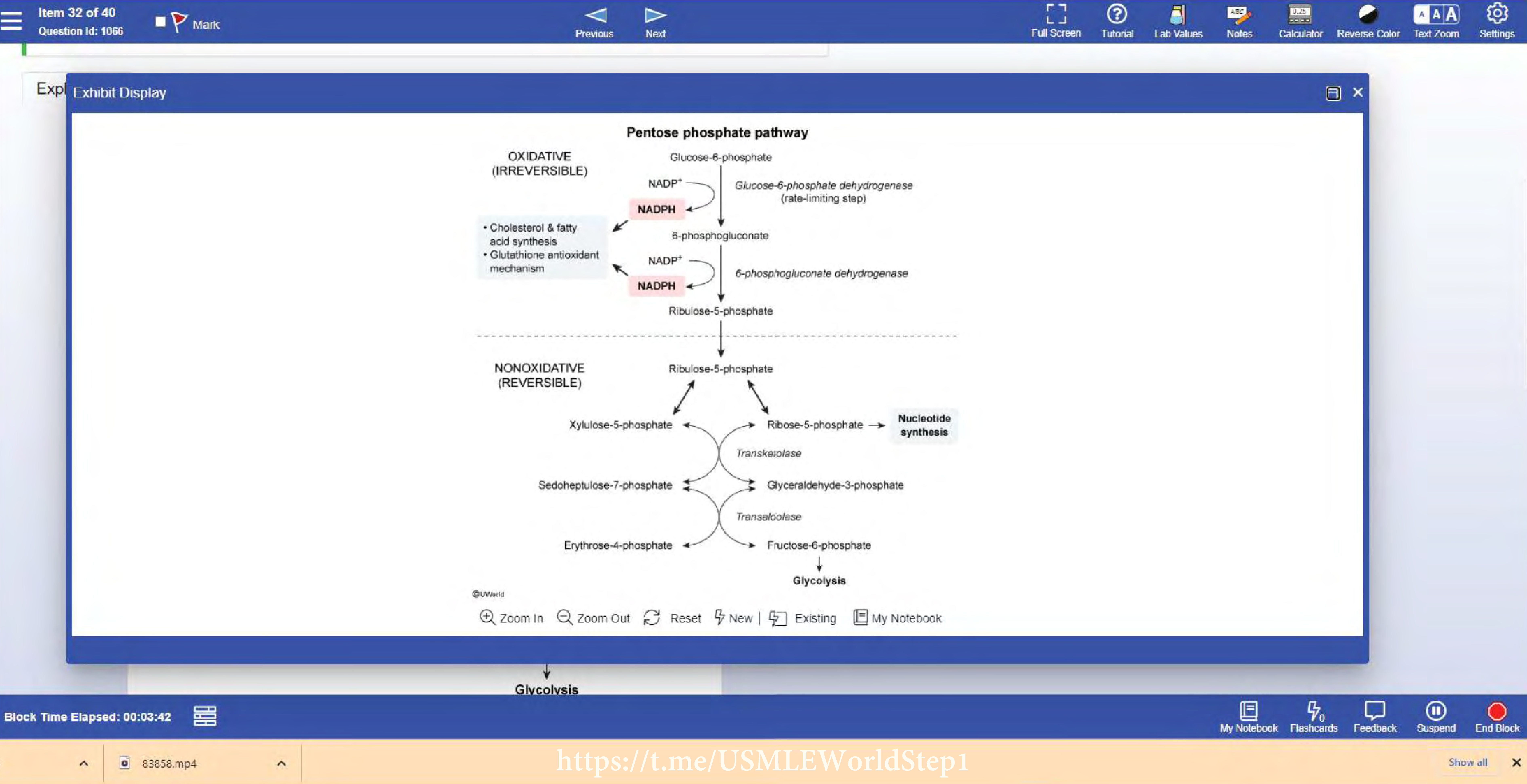
Item 32 of 40
Question Id: 1066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Pentose phosphate pathway
OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP+
NADPH
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
• Cholesterol & fatty acid synthesis
• Glutathione antioxidant mechanism
6-phosphogluconate
NADP+
NADPH
6-phosphogluconate dehydrogenase
Ribulose-5-phosphate
NONOXIDATIVE
(REVERSIBLE)
Ribulose-5-phosphate
Xylulose-5-phosphate
Ribose-5-phosphate
Nucleotide synthesis
Transketolase
Sedoheptulose-7-phosphate
Glyceraldehyde-3-phosphate
Transaldolase
Erythrose-4-phosphate
Fructose-6-phosphate
Glycolysis
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Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Glycolysis
Block Time Elapsed: 00:03:42
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Item 32 of 40
Question Id: 1066

This patient most likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD catalyzes the first step in the pentose phosphate pathway (PPP), the oxidative portion of which generates 2 molecules of NADPH while converting glucose-6-phosphate to ribulose-5-phosphate. The nonoxidative reactions of the PPP reversibly convert ribulose-5-phosphate into ribose-5-phosphate (substrate for nucleotide synthesis) or glycolytic intermediates that can be used for energy production.

Because the PPP is the **main source of NADPH**, the pathway is particularly active in:

- Cells experiencing **high oxidative stress** (eg, erythrocytes) in which NADPH is used to regenerate reduced glutathione, an antioxidant that helps maintain cell integrity
- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids) and cytochrome P450 metabolism
- Phagocytic cells generating a respiratory burst via NADPH oxidase

In patients with G6PD deficiency, erythrocytes are unable to maintain a sufficient supply of reduced glutathione during periods of increased oxidative stress, which can occur with certain infections (eg, pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa drugs). The resulting oxidative damage causes **acute hemolytic anemia** and jaundice.

(Choice A) NADH can be used as a reducing agent to convert ADP to ATP during oxidative phosphorylation. In contrast to NADH, NADPH cannot be used to convert ADP into ATP.

(Choice C) Glycogenesis is the process by which glucose is stored for later use through the addition of glucose molecules to glycogen chains. It does not require NADPH.

(Choice D) Ketone bodies are formed mainly in the liver during times of fasting when there is increased fat degradation. Cytosolic HMG-CoA synthase is the starting point of cholesterol synthesis whereas the mitochondrial version of the enzyme is the rate-limiting step in ketone body synthesis. Unlike cholesterol synthesis, ketone body production does not require NADPH.

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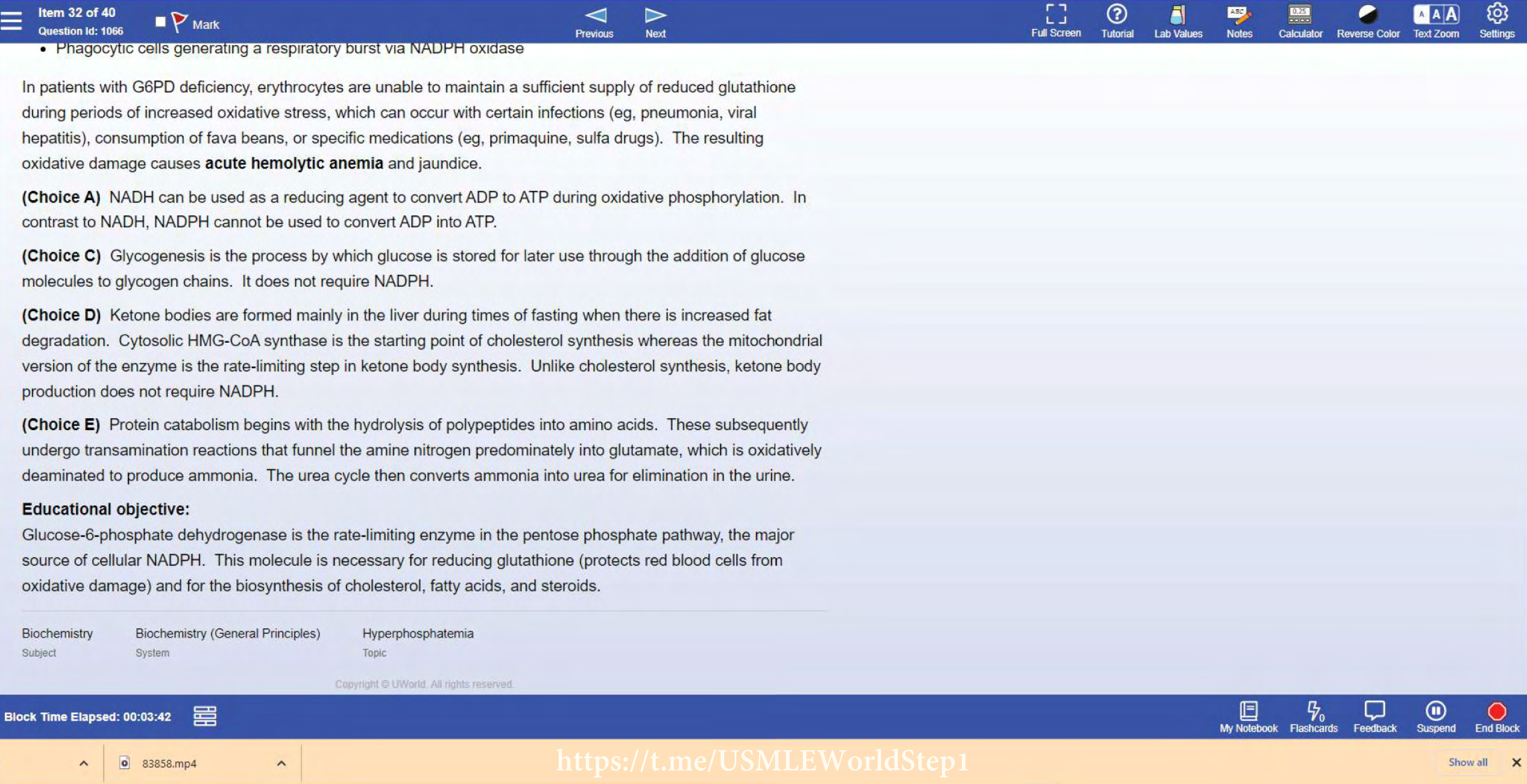
Item 32 of 40
Question Id: 1066
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

- Phagocytic cells generating a respiratory burst via NADPH oxidase

In patients with G6PD deficiency, erythrocytes are unable to maintain a sufficient supply of reduced glutathione during periods of increased oxidative stress, which can occur with certain infections (eg, pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa drugs). The resulting oxidative damage causes **acute hemolytic anemia** and jaundice.

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(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

Educational objective:

Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the major source of cellular NADPH. This molecule is necessary for reducing glutathione (protects red blood cells from oxidative damage) and for the biosynthesis of cholesterol, fatty acids, and steroids.

Biochemistry	Biochemistry (General Principles)	Hyperphosphatemia
Subject	System	Topic

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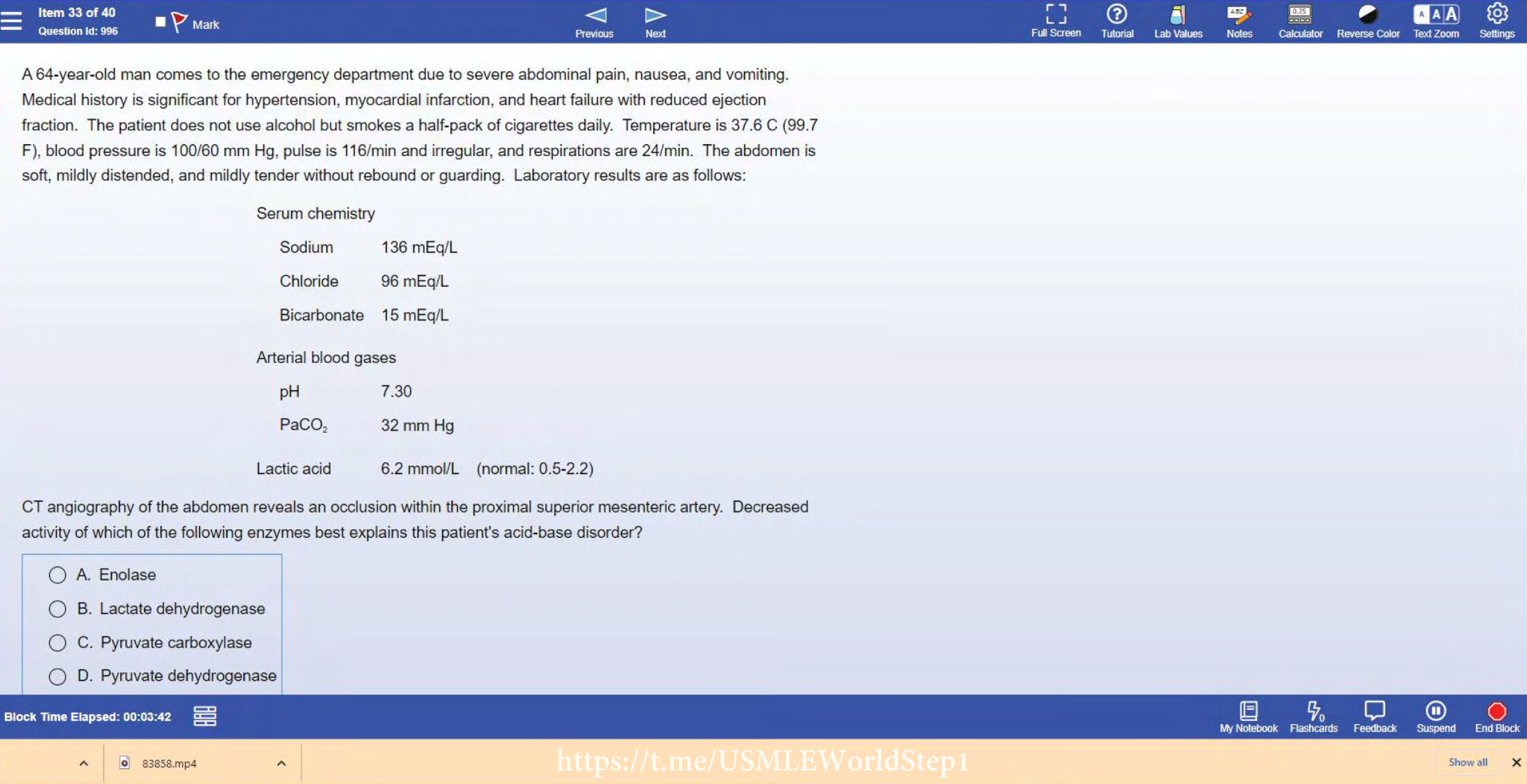
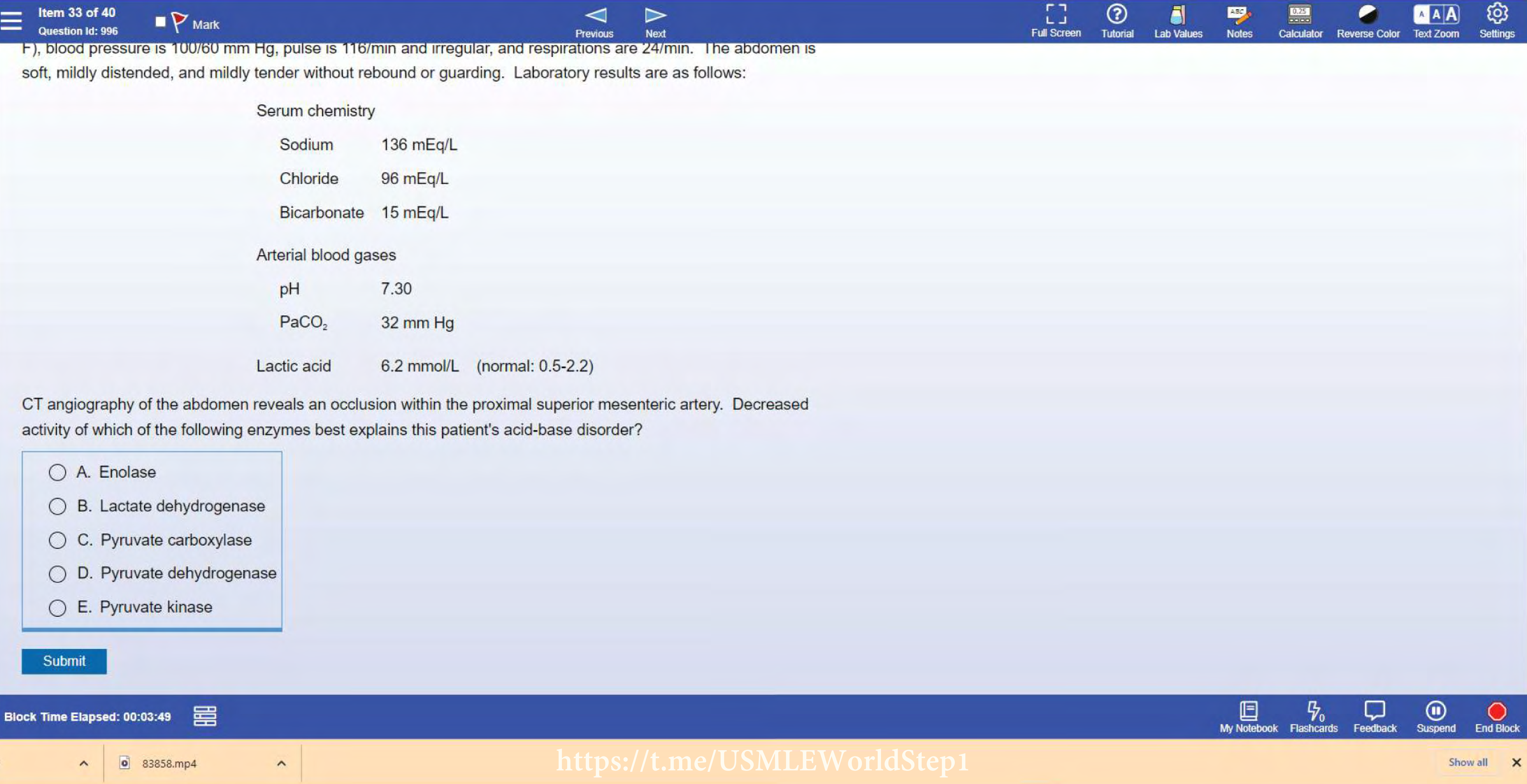

Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:42
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

A 64-year-old man comes to the emergency department due to severe abdominal pain, nausea, and vomiting. Medical history is significant for hypertension, myocardial infarction, and heart failure with reduced ejection fraction. The patient does not use alcohol but smokes a half-pack of cigarettes daily. Temperature is 37.6 C (99.7 F), blood pressure is 100/60 mm Hg, pulse is 116/min and irregular, and respirations are 24/min. The abdomen is soft, mildly distended, and mildly tender without rebound or guarding. Laboratory results are as follows:

Serum chemistry		
Sodium	136 mEq/L	
Chloride	96 mEq/L	
Bicarbonate	15 mEq/L	
Arterial blood gases		
pH	7.30	
$PaCO_2$	32 mm Hg	
Lactic acid	6.2 mmol/L	(normal: 0.5-2.2)

CT angiography of the abdomen reveals an occlusion within the proximal superior mesenteric artery. Decreased activity of which of the following enzymes best explains this patient's acid-base disorder?

○ A. Enolase
○ B. Lactate dehydrogenase
○ C. Pyruvate carboxylase
○ D. Pyruvate dehydrogenase


Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:49
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

F), blood pressure is 100/60 mm Hg, pulse is 116/min and irregular, and respirations are 24/min. The abdomen is soft, mildly distended, and mildly tender without rebound or guarding. Laboratory results are as follows:

Serum chemistry	
Sodium	136 mEq/L
Chloride	96 mEq/L
Bicarbonate	15 mEq/L
Arterial blood gases	
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○ A. Enolase
○ B. Lactate dehydrogenase
○ C. Pyruvate carboxylase
○ D. Pyruvate dehydrogenase
○ E. Pyruvate kinase

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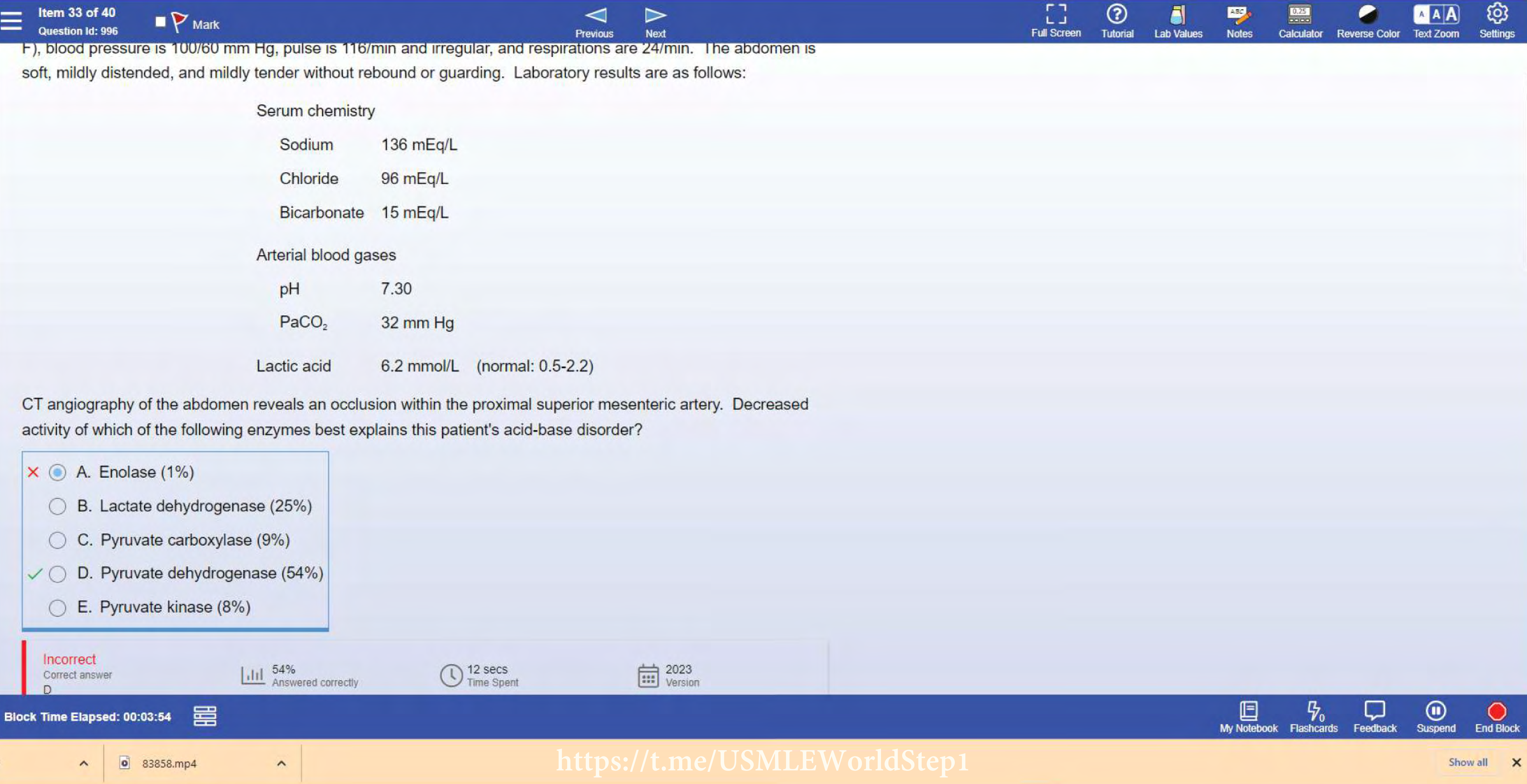
Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Bicarbonate	15 mEq/L
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pH	7.30
$PaCO_2$	32 mm Hg
Lactic acid	6.2 mmol/L (normal: 0.5-2.2)

CT angiography of the abdomen reveals an occlusion within the proximal superior mesenteric artery. Decreased activity of which of the following enzymes best explains this patient's acid-base disorder?

✗ ● A. Enolase (1%)
○ B. Lactate dehydrogenase (25%)
○ C. Pyruvate carboxylase (9%)
✓ ○ D. Pyruvate dehydrogenase (54%)
○ E. Pyruvate kinase (8%)

Incorrect
Correct answer
D

54%
Answered correctly

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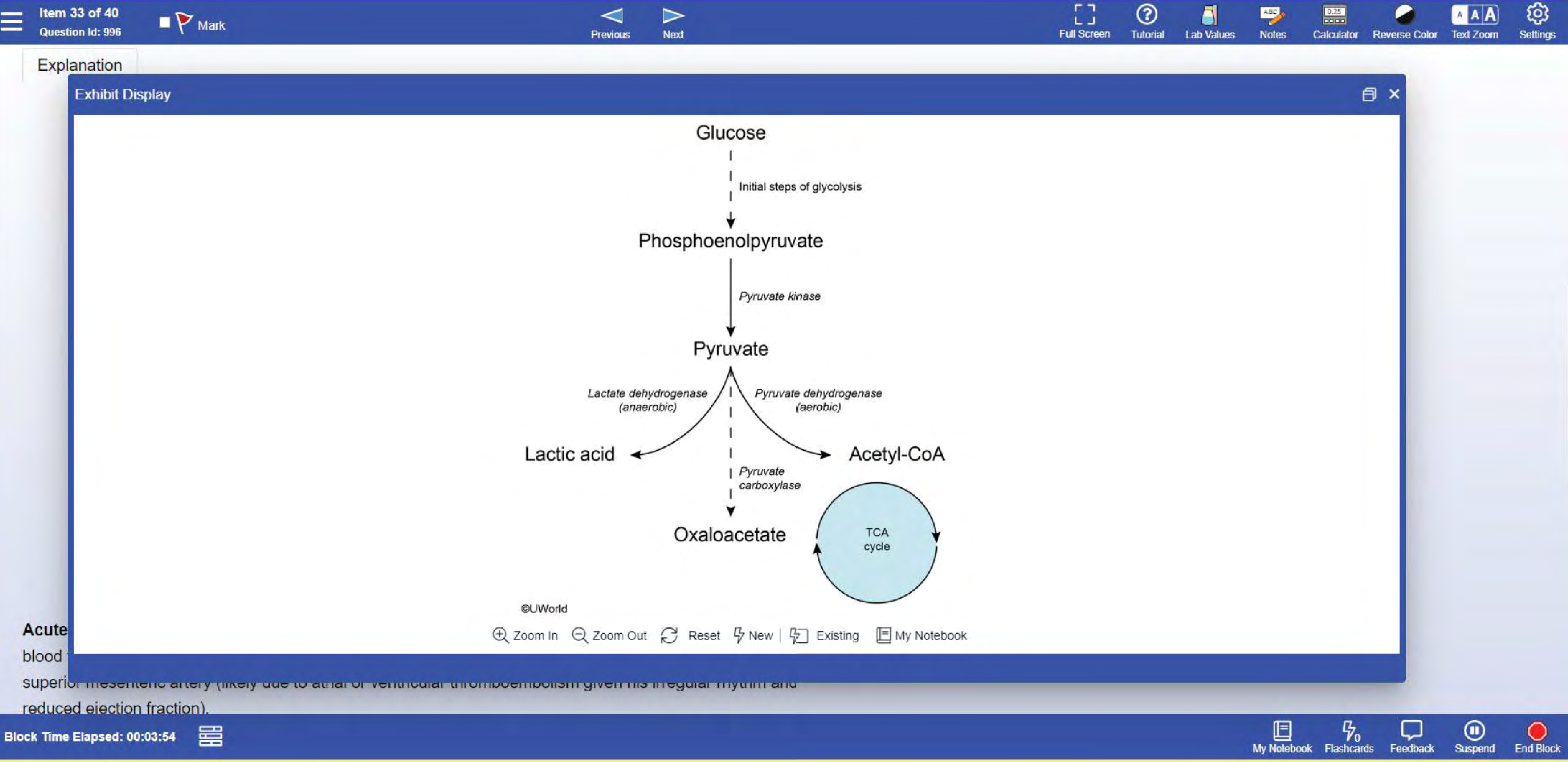
2023
Version

Block Time Elapsed: 00:03:54

My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all


Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Glucose
Initial steps of glycolysis
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
Lactate dehydrogenase (anaerobic)
Pyruvate dehydrogenase (aerobic)
Lactic acid
Acetyl-CoA
Pyruvate carboxylase
Oxaloacetate
TCA cycle
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Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:03:54
My Notebook
Flashcards
Feedback
Suspend
End Block

Acute

blood

superior mesenteric artery (likely due to atrial or ventricular thromboembolism given his irregular rhythm and reduced ejection fraction).

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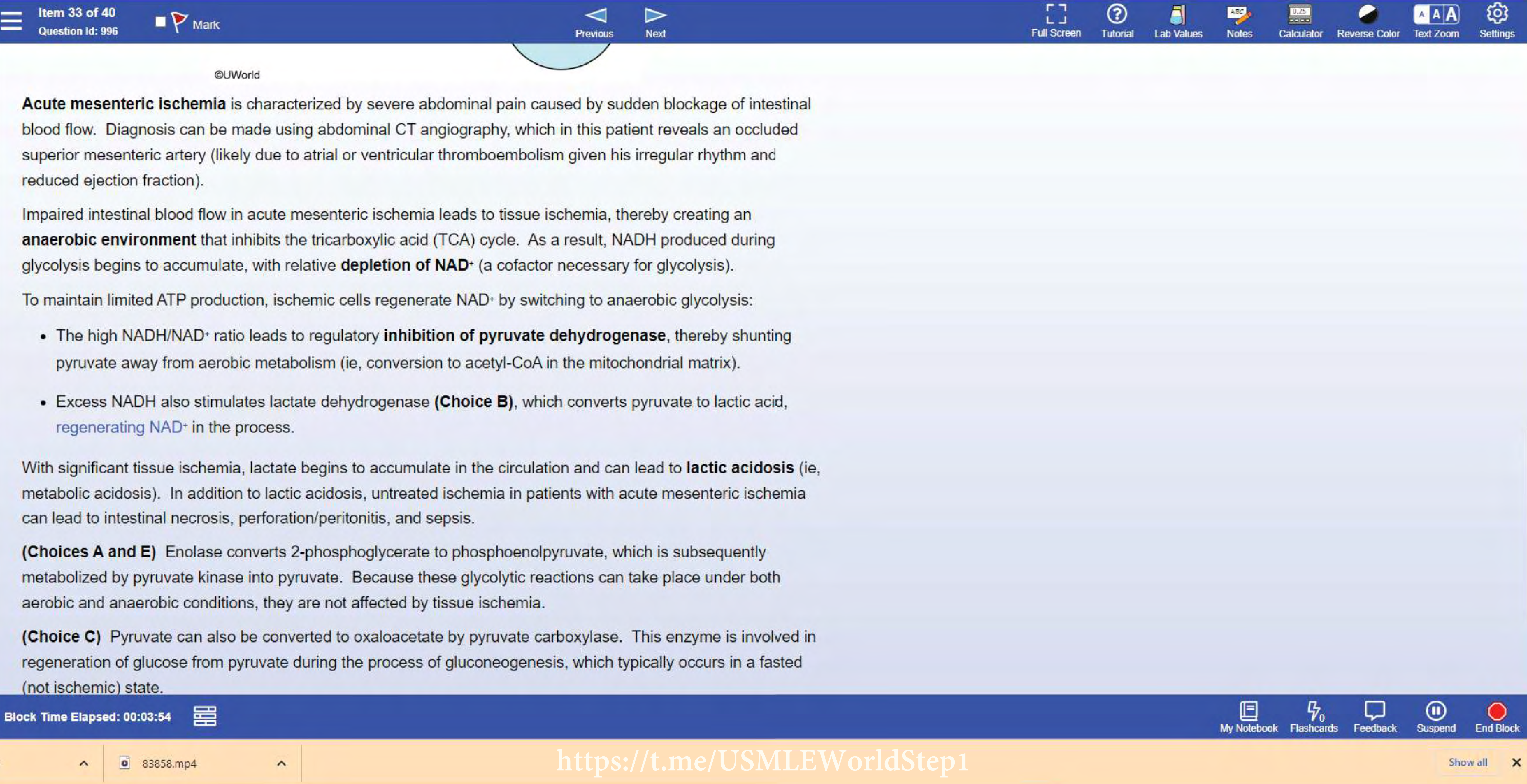
Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Acute mesenteric ischemia is characterized by severe abdominal pain caused by sudden blockage of intestinal blood flow. Diagnosis can be made using abdominal CT angiography, which in this patient reveals an occluded superior mesenteric artery (likely due to atrial or ventricular thromboembolism given his irregular rhythm and reduced ejection fraction).

Impaired intestinal blood flow in acute mesenteric ischemia leads to tissue ischemia, thereby creating an **anaerobic environment** that inhibits the tricarboxylic acid (TCA) cycle. As a result, NADH produced during glycolysis begins to accumulate, with relative **depletion of NAD^+** (a cofactor necessary for glycolysis).

To maintain limited ATP production, ischemic cells regenerate NAD^+ by switching to anaerobic glycolysis:

- The high NADH/NAD^+ ratio leads to regulatory **inhibition of pyruvate dehydrogenase**, thereby shunting pyruvate away from aerobic metabolism (ie, conversion to acetyl-CoA in the mitochondrial matrix).
- Excess NADH also stimulates lactate dehydrogenase **(Choice B)**, which converts pyruvate to lactic acid, regenerating NAD^+ in the process.

With significant tissue ischemia, lactate begins to accumulate in the circulation and can lead to **lactic acidosis** (ie, metabolic acidosis). In addition to lactic acidosis, untreated ischemia in patients with acute mesenteric ischemia can lead to intestinal necrosis, perforation/peritonitis, and sepsis.

(Choices A and E) Enolase converts 2-phosphoglycerate to phosphoenolpyruvate, which is subsequently metabolized by pyruvate kinase into pyruvate. Because these glycolytic reactions can take place under both aerobic and anaerobic conditions, they are not affected by tissue ischemia.

(Choice C) Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase. This enzyme is involved in regeneration of glucose from pyruvate during the process of gluconeogenesis, which typically occurs in a fasted (not ischemic) state.

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My Notebook
Flashcards
Feedback
Suspend
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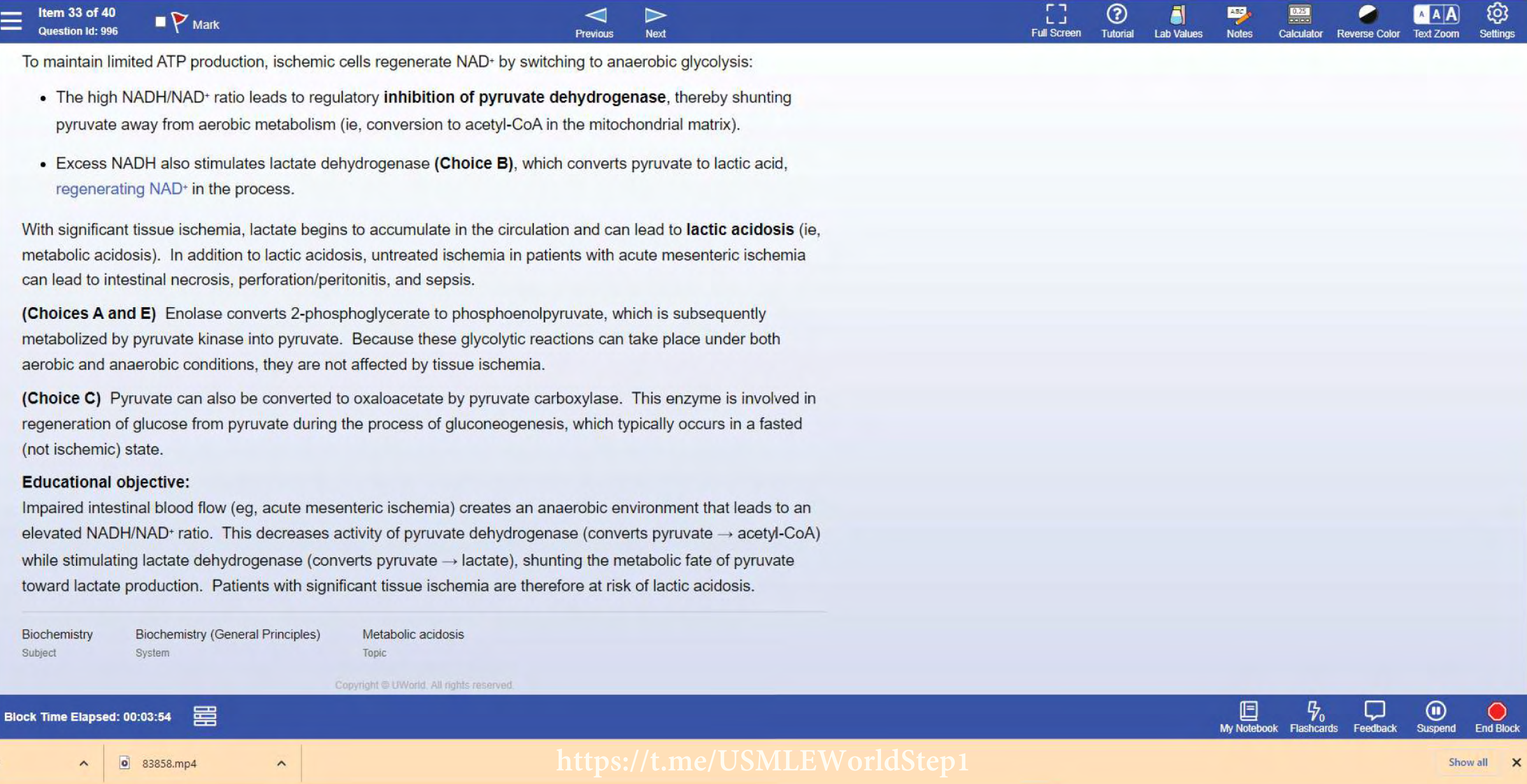
Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choice C) Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase. This enzyme is involved in regeneration of glucose from pyruvate during the process of gluconeogenesis, which typically occurs in a fasted (not ischemic) state.

Educational objective:

Impaired intestinal blood flow (eg, acute mesenteric ischemia) creates an anaerobic environment that leads to an elevated $NADH/NAD^+$ ratio. This decreases activity of pyruvate dehydrogenase (converts pyruvate → acetyl-CoA) while stimulating lactate dehydrogenase (converts pyruvate → lactate), shunting the metabolic fate of pyruvate toward lactate production. Patients with significant tissue ischemia are therefore at risk of lactic acidosis.

Biochemistry	Biochemistry (General Principles)	Metabolic acidosis
Subject	System	Topic

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My Notebook
Flashcards
Feedback
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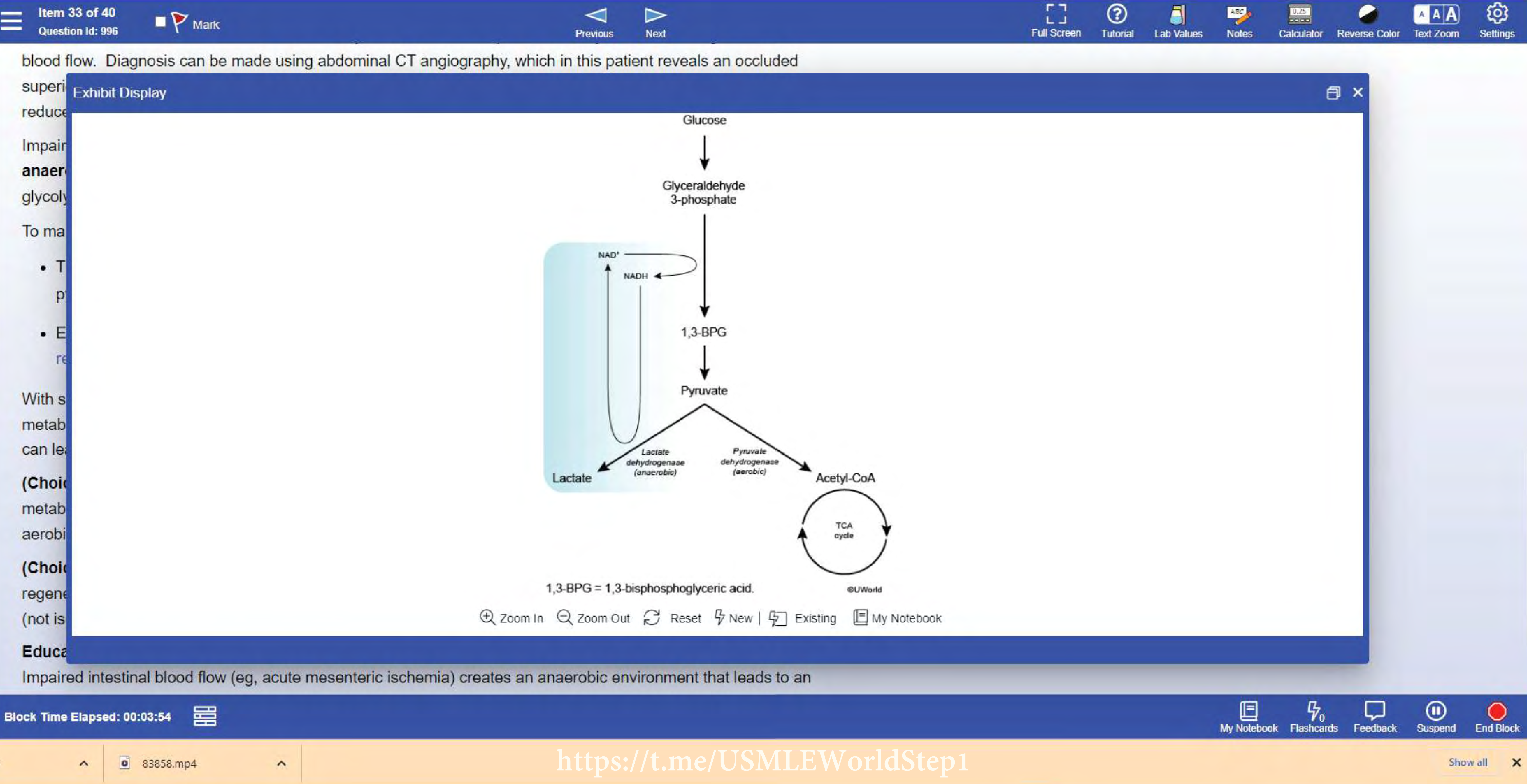
Item 33 of 40
Question Id: 996
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Glucose
Glyceraldehyde 3-phosphate
NAD⁺
NADH
1,3-BPG
Pyruvate
Lactate dehydrogenase (anaerobic)
Pyruvate dehydrogenase (aerobic)
Lactate
Acetyl-CoA
TCA cycle
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Zoom In
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My Notebook
Block Time Elapsed: 00:03:54
My Notebook
Flashcards
Feedback
Suspend
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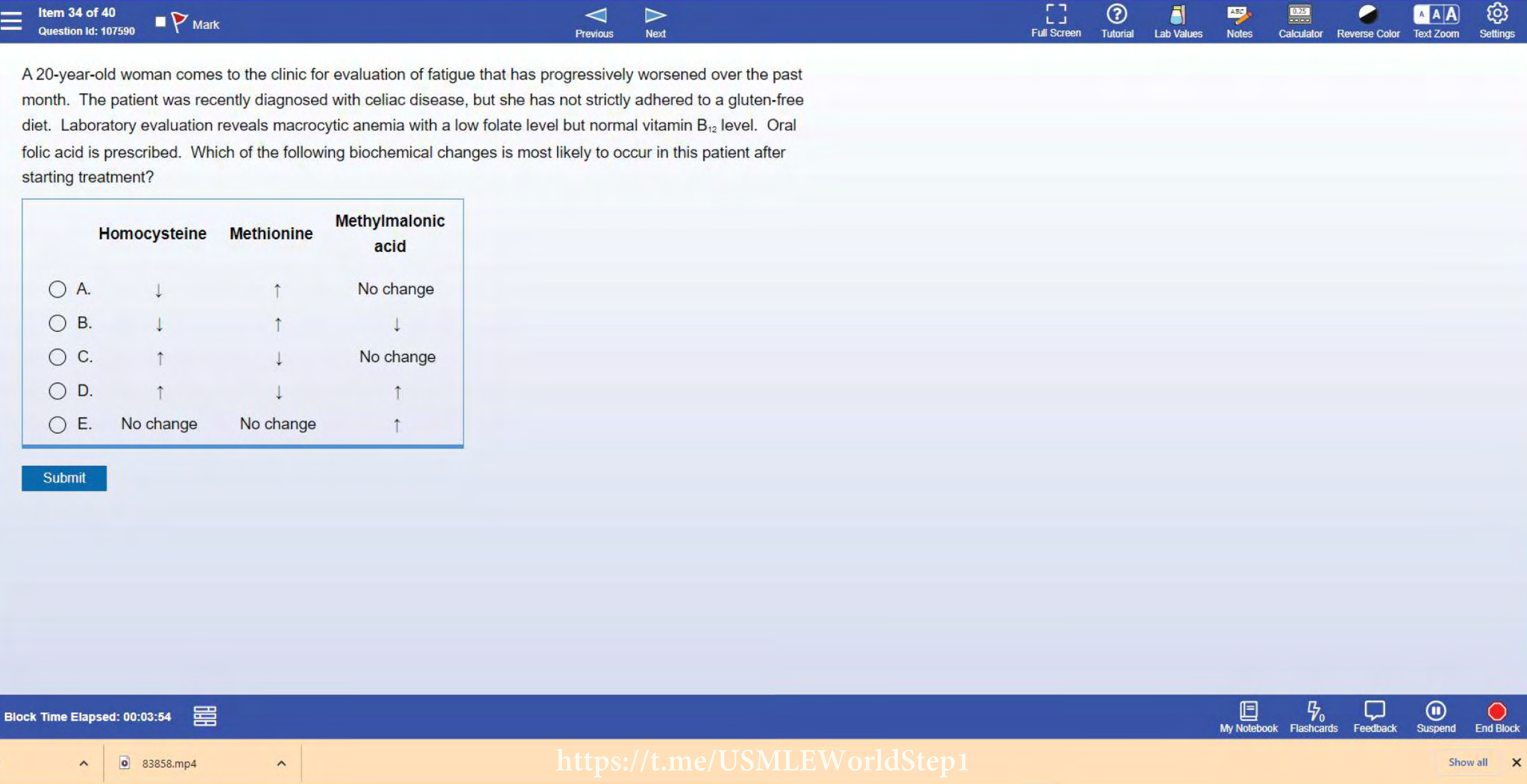
Impaired intestinal blood flow (eg, acute mesenteric ischemia) creates an anaerobic environment that leads to an

1,3-BPG = 1,3-bisphosphoglyceric acid.


Item 34 of 40
Question Id: 107590
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 20-year-old woman comes to the clinic for evaluation of fatigue that has progressively worsened over the past month. The patient was recently diagnosed with celiac disease, but she has not strictly adhered to a gluten-free diet. Laboratory evaluation reveals macrocytic anemia with a low folate level but normal vitamin B_{12} level. Oral folic acid is prescribed. Which of the following biochemical changes is most likely to occur in this patient after starting treatment?

	Homocysteine	Methionine	Methylmalonic acid
○ A.	↓	↑	No change
○ B.	↓	↑	↓
○ C.	↑	↓	No change
○ D.	↑	↓	↑
○ E.	No change	No change	↑

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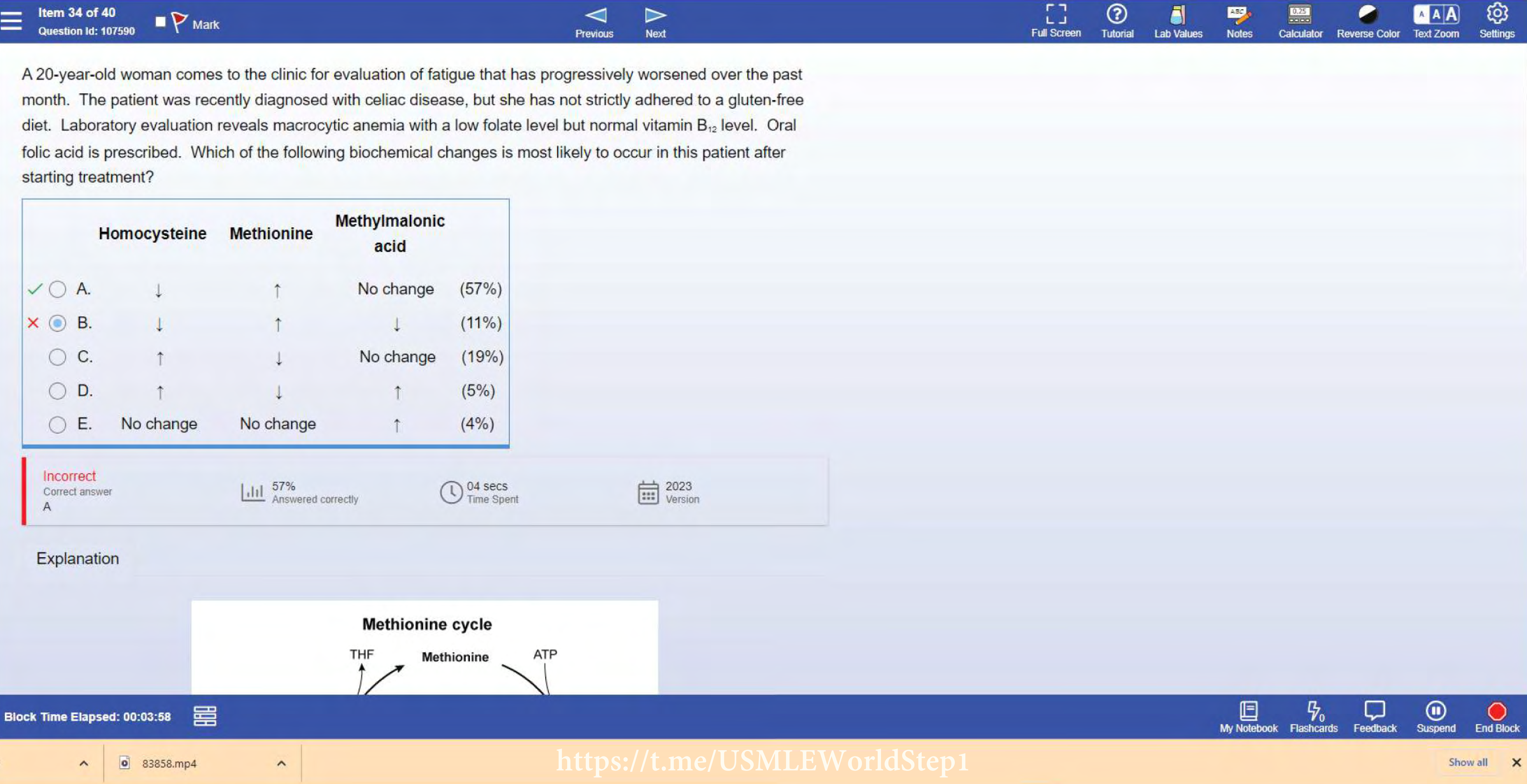
Block Time Elapsed: 00:03:54
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all


Item 34 of 40
Question Id: 107590
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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	Homocysteine	Methionine	Methylmalonic acid	
✓ ○ A.	↓	↑	No change	(57%)
✗ ● B.	↓	↑	↓	(11%)
○ C.	↑	↓	No change	(19%)
○ D.	↑	↓	↑	(5%)
○ E.	No change	No change	↑	(4%)

Incorrect
Correct answer
A

57%
Answered correctly

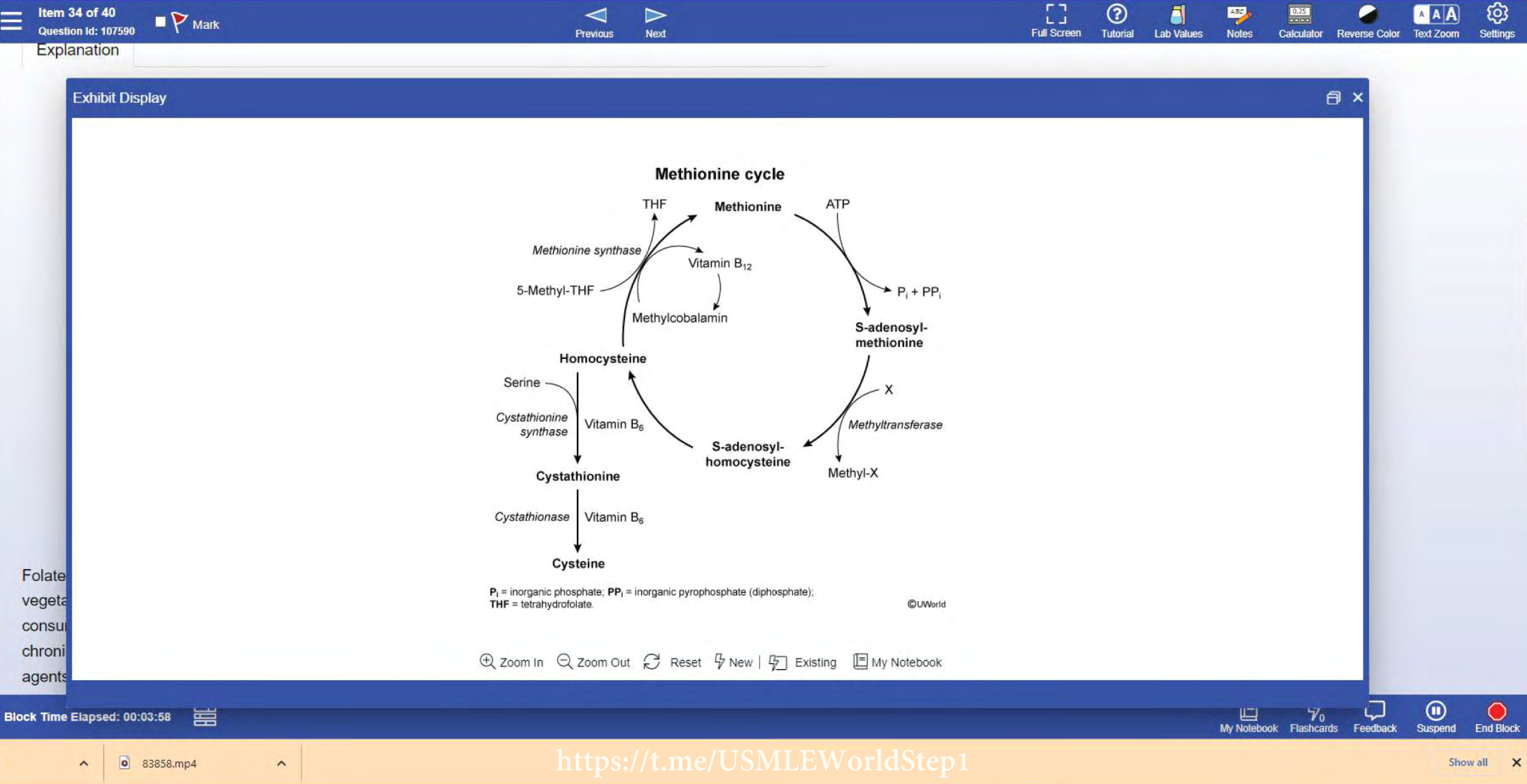
04 secs
Time Spent

2023
Version

Explanation

Methionine cycle

THF
Methionine
ATP
Block Time Elapsed: 00:03:58
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all


Item 34 of 40
Question Id: 107590
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Methionine cycle
THF
Methionine
ATP
Methionine synthase
Vitamin B12
5-Methyl-THF
Methylcobalamin
P_i + PP_i
S-adenosyl-methionine
Homocysteine
Serine
X
Cystathionine synthase
Vitamin B6
Methyltransferase
S-adenosyl-homocysteine
Methyl-X
Cystathionine
Cystathionase
Vitamin B6
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New
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My Notebook
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P_i = inorganic phosphate; **PP_i** = inorganic pyrophosphate (diphosphate); **THF** = tetrahydrofolate.

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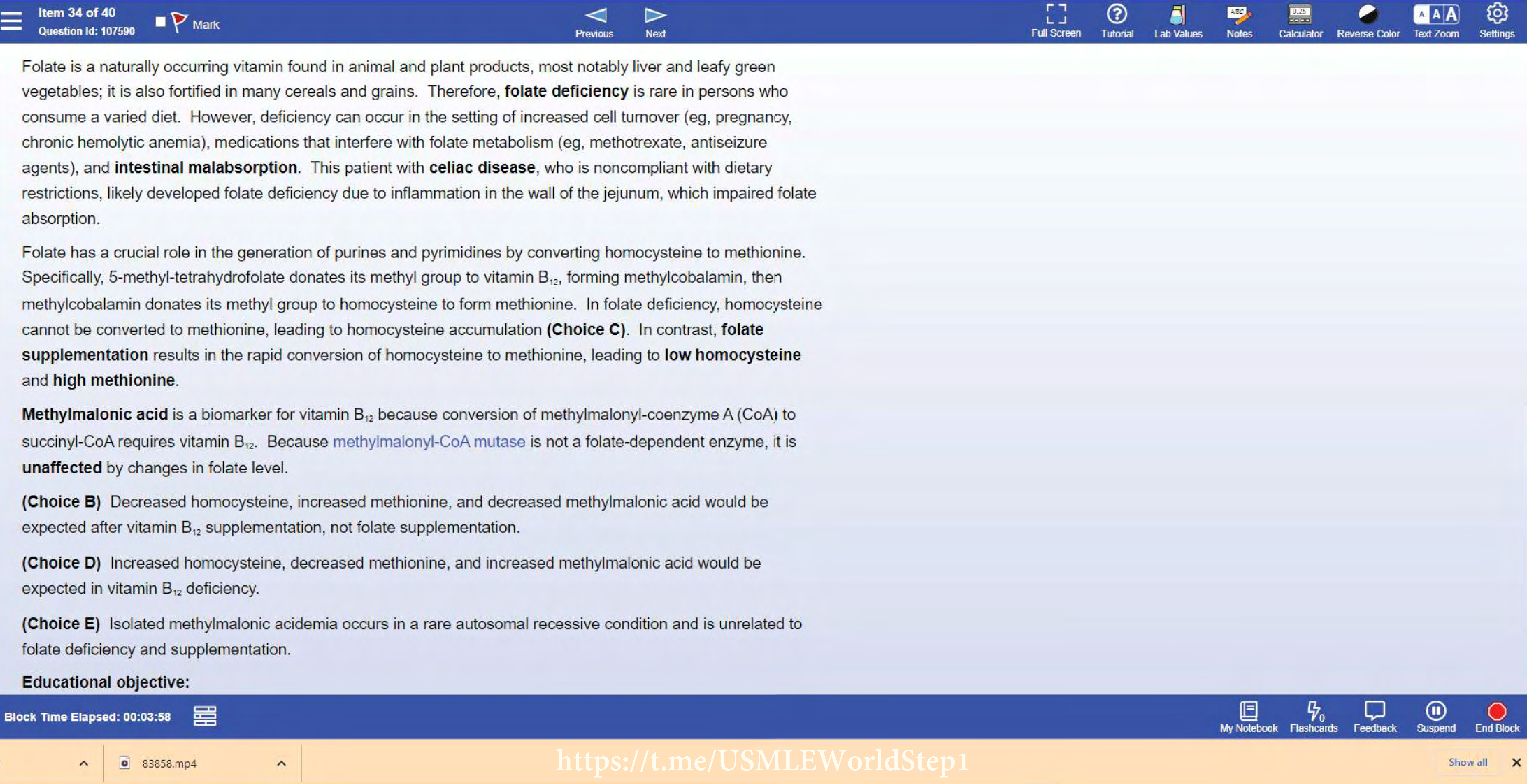
Item 34 of 40
Question Id: 107590
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Folate is a naturally occurring vitamin found in animal and plant products, most notably liver and leafy green vegetables; it is also fortified in many cereals and grains. Therefore, **folate deficiency** is rare in persons who consume a varied diet. However, deficiency can occur in the setting of increased cell turnover (eg, pregnancy, chronic hemolytic anemia), medications that interfere with folate metabolism (eg, methotrexate, antiseizure agents), and **intestinal malabsorption**. This patient with **celiac disease**, who is noncompliant with dietary restrictions, likely developed folate deficiency due to inflammation in the wall of the jejunum, which impaired folate absorption.

Folate has a crucial role in the generation of purines and pyrimidines by converting homocysteine to methionine. Specifically, 5-methyl-tetrahydrofolate donates its methyl group to vitamin B_{12}, forming methylcobalamin, then methylcobalamin donates its methyl group to homocysteine to form methionine. In folate deficiency, homocysteine cannot be converted to methionine, leading to homocysteine accumulation **(Choice C)**. In contrast, **folate supplementation** results in the rapid conversion of homocysteine to methionine, leading to **low homocysteine** and **high methionine**.

Methylmalonic acid is a biomarker for vitamin B_{12} because conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA requires vitamin B_{12}. Because methylmalonyl-CoA mutase is not a folate-dependent enzyme, it is **unaffected** by changes in folate level.

(Choice B) Decreased homocysteine, increased methionine, and decreased methylmalonic acid would be expected after vitamin B_{12} supplementation, not folate supplementation.

(Choice D) Increased homocysteine, decreased methionine, and increased methylmalonic acid would be expected in vitamin B_{12} deficiency.

(Choice E) Isolated methylmalonic acidemia occurs in a rare autosomal recessive condition and is unrelated to folate deficiency and supplementation.

Educational objective:

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My Notebook
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Feedback
Suspend
End Block
83858.mp4
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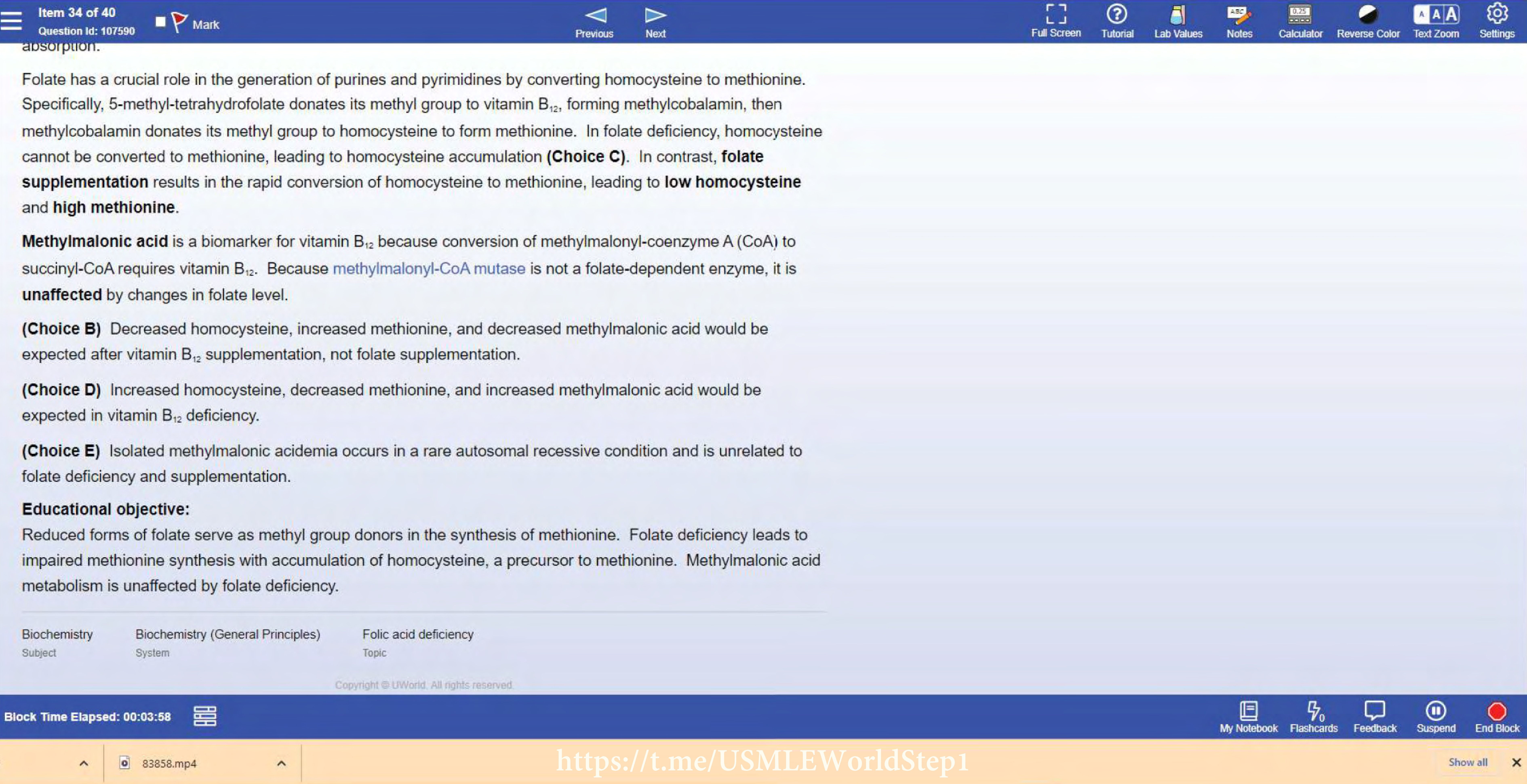
Item 34 of 40
Question Id: 107590
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

absorption.

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(Choice E) Isolated methylmalonic acidemia occurs in a rare autosomal recessive condition and is unrelated to folate deficiency and supplementation.

Educational objective:

Reduced forms of folate serve as methyl group donors in the synthesis of methionine. Folate deficiency leads to impaired methionine synthesis with accumulation of homocysteine, a precursor to methionine. Methylmalonic acid metabolism is unaffected by folate deficiency.

Biochemistry	Biochemistry (General Principles)	Folic acid deficiency
Subject	System	Topic

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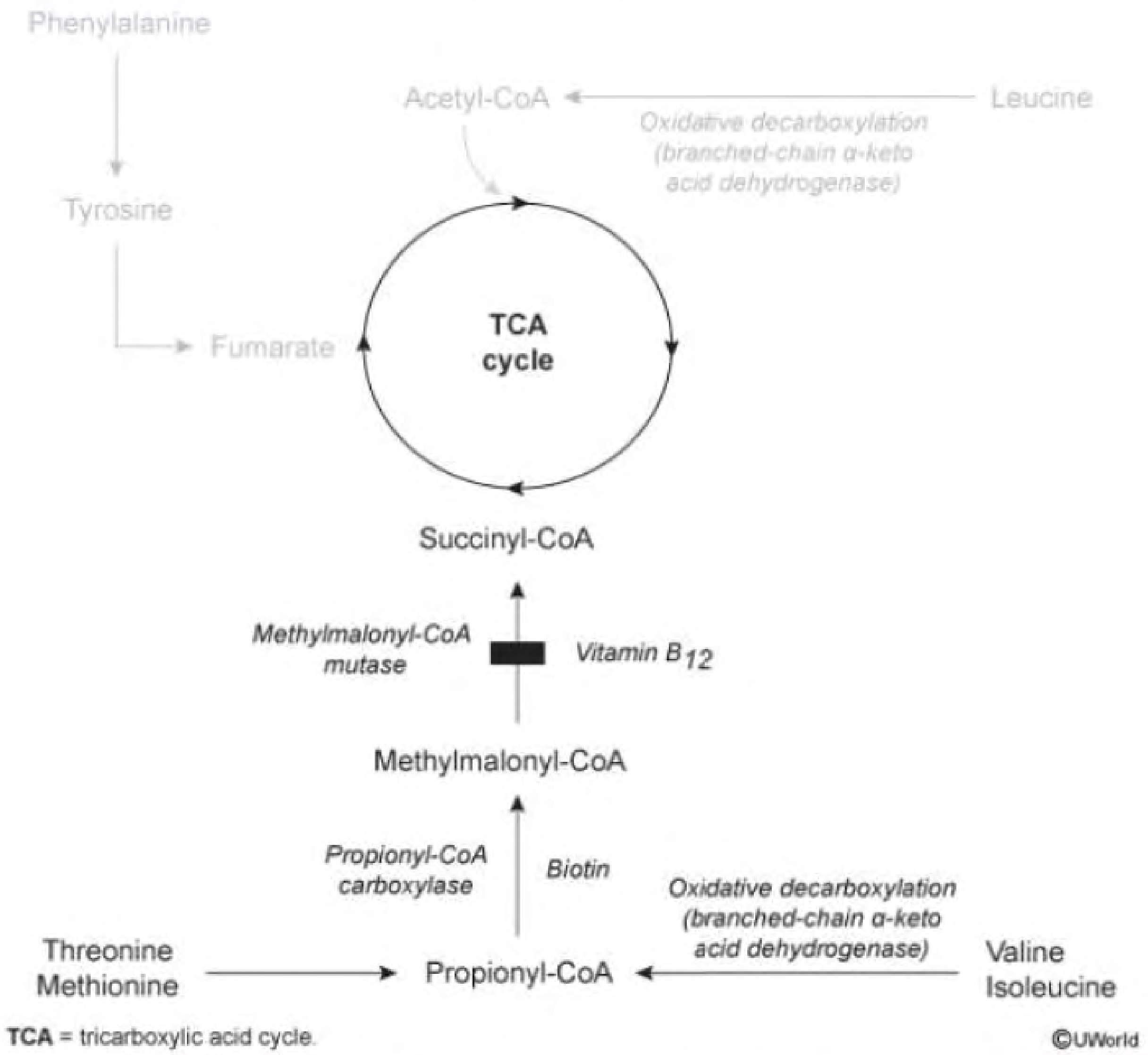
Methylmalonic acidemia


Phenylalanine
Acetyl-CoA
Leucine
Oxidative decarboxylation (branched-chain α-keto acid dehydrogenase)
Tyrosine
Fumarate
TCA cycle
Succinyl-CoA
Methylmalonyl-CoA mutase
Vitamin B12
Methylmalonyl-CoA
Propionyl-CoA carboxylase
Biotin
Oxidative decarboxylation (branched-chain α-keto acid dehydrogenase)
Threonine
Methionine
Propionyl-CoA
Valine
Isoleucine
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TCA = tricarboxylic acid cycle.

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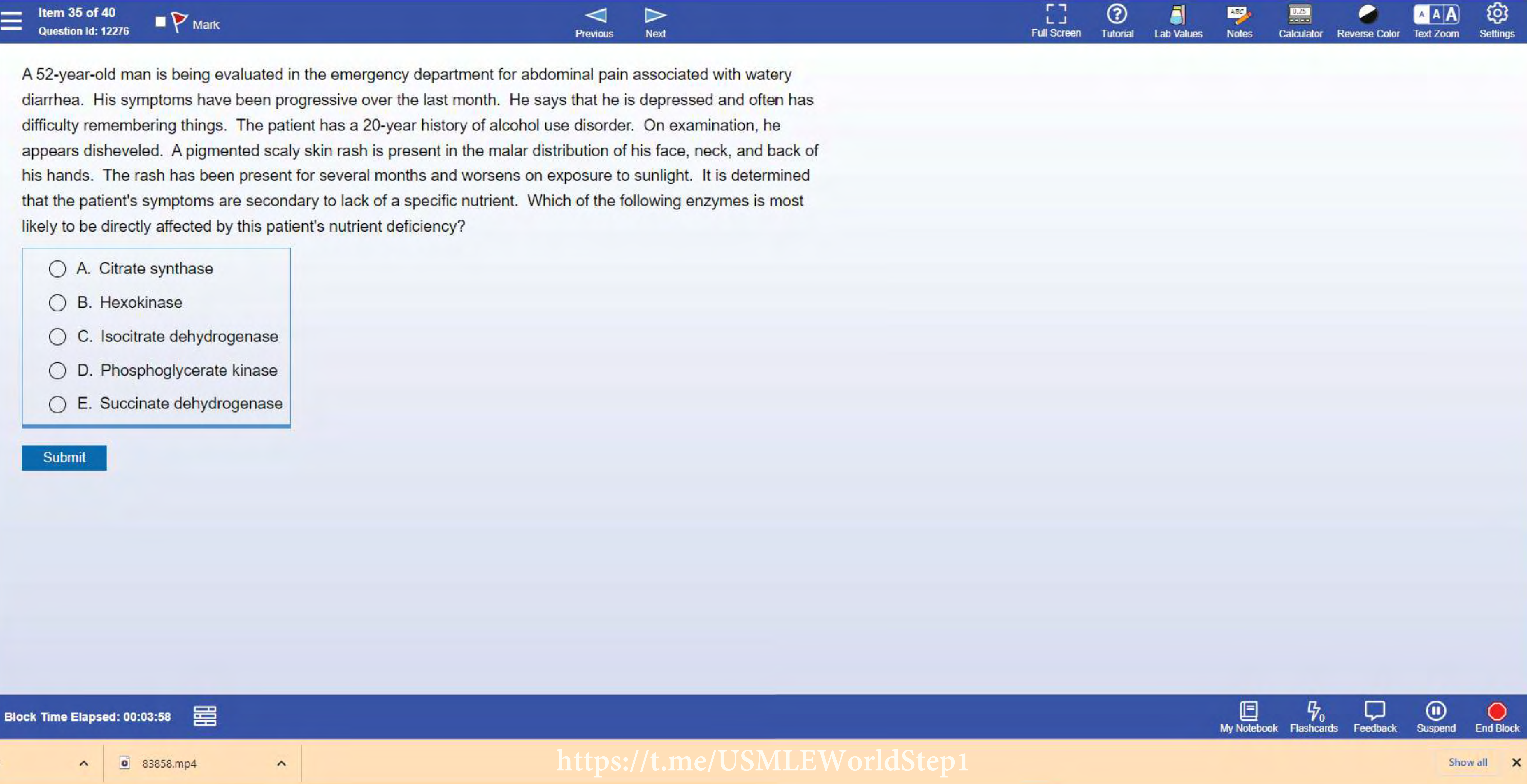
Item 35 of 40
Question Id: 12276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:58
My Notebook
Flashcards
Feedback
Suspend
End Block
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Show all

A 52-year-old man is being evaluated in the emergency department for abdominal pain associated with watery diarrhea. His symptoms have been progressive over the last month. He says that he is depressed and often has difficulty remembering things. The patient has a 20-year history of alcohol use disorder. On examination, he appears disheveled. A pigmented scaly skin rash is present in the malar distribution of his face, neck, and back of his hands. The rash has been present for several months and worsens on exposure to sunlight. It is determined that the patient's symptoms are secondary to lack of a specific nutrient. Which of the following enzymes is most likely to be directly affected by this patient's nutrient deficiency?

- ○ A. Citrate synthase
- ○ B. Hexokinase
- ○ C. Isocitrate dehydrogenase
- ○ D. Phosphoglycerate kinase
- ○ E. Succinate dehydrogenase

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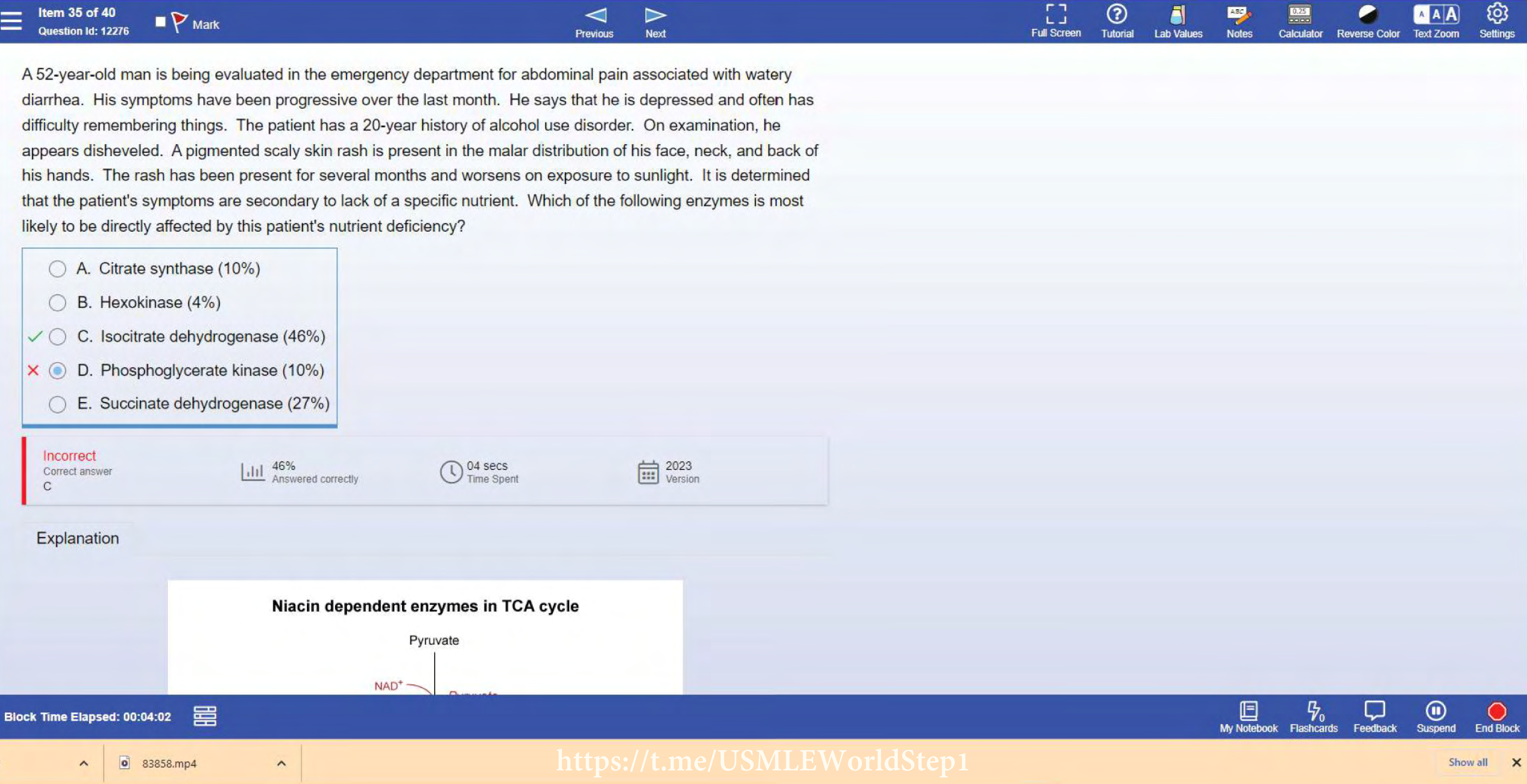
Item 35 of 40
Question Id: 12276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Citrate synthase (10%)
○ B. Hexokinase (4%)
✓ ○ C. Isocitrate dehydrogenase (46%)
✗ ● D. Phosphoglycerate kinase (10%)
○ E. Succinate dehydrogenase (27%)

Incorrect
Correct answer
C

46%
Answered correctly

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2023
Version

Explanation

Niacin dependent enzymes in TCA cycle

Pyruvate
NAD⁺
Pyruvate

Block Time Elapsed: 00:04:02
My Notebook
Flashcards
Feedback
Suspend
End Block
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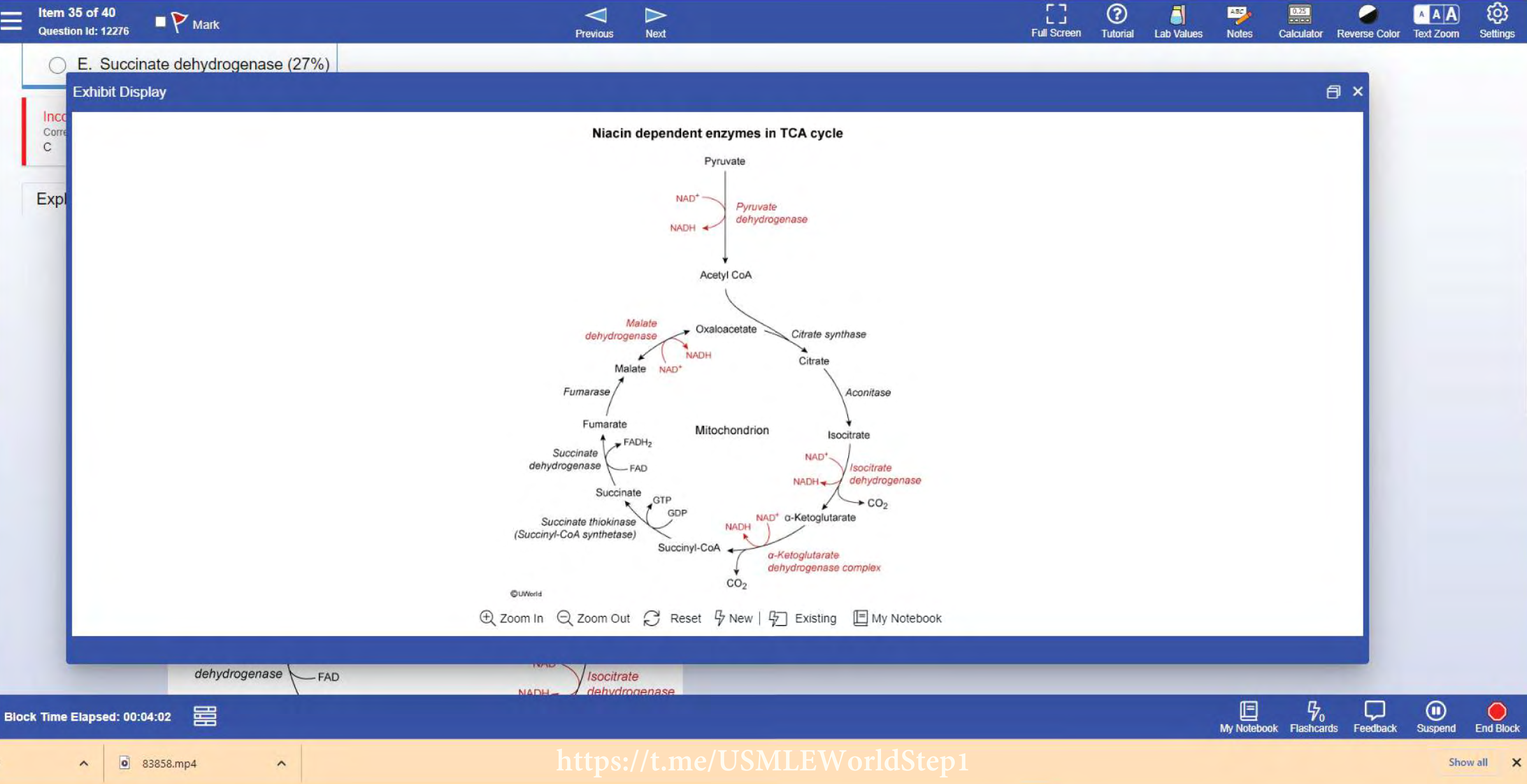
Item 35 of 40
Question Id: 12276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

○ E. Succinate dehydrogenase (27%)

Exhibit Display

Niacin dependent enzymes in TCA cycle

Pyruvate
NAD$^+$
NADH
Pyruvate dehydrogenase
Acetyl CoA
Oxaloacetate
Citrate synthase
Citrate
Aconitase
Isocitrate
NAD$^+$
NADH
Isocitrate dehydrogenase
CO$_2$
α-Ketoglutarate
NAD$^+$
NADH
α-Ketoglutarate dehydrogenase complex
CO$_2$
Succinyl-CoA
Succinate thiokinase (Succinyl-CoA synthetase)
GTP
GDP
Succinate
Succinate dehydrogenase
FAD
FADH$_2$
Fumarate
Fumarase
Malate
Malate dehydrogenase
NAD$^+$
NADH
Mitochondrion
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Zoom Out
Reset
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My Notebook
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Flashcards
Feedback
Suspend
End Block
83858.mp4
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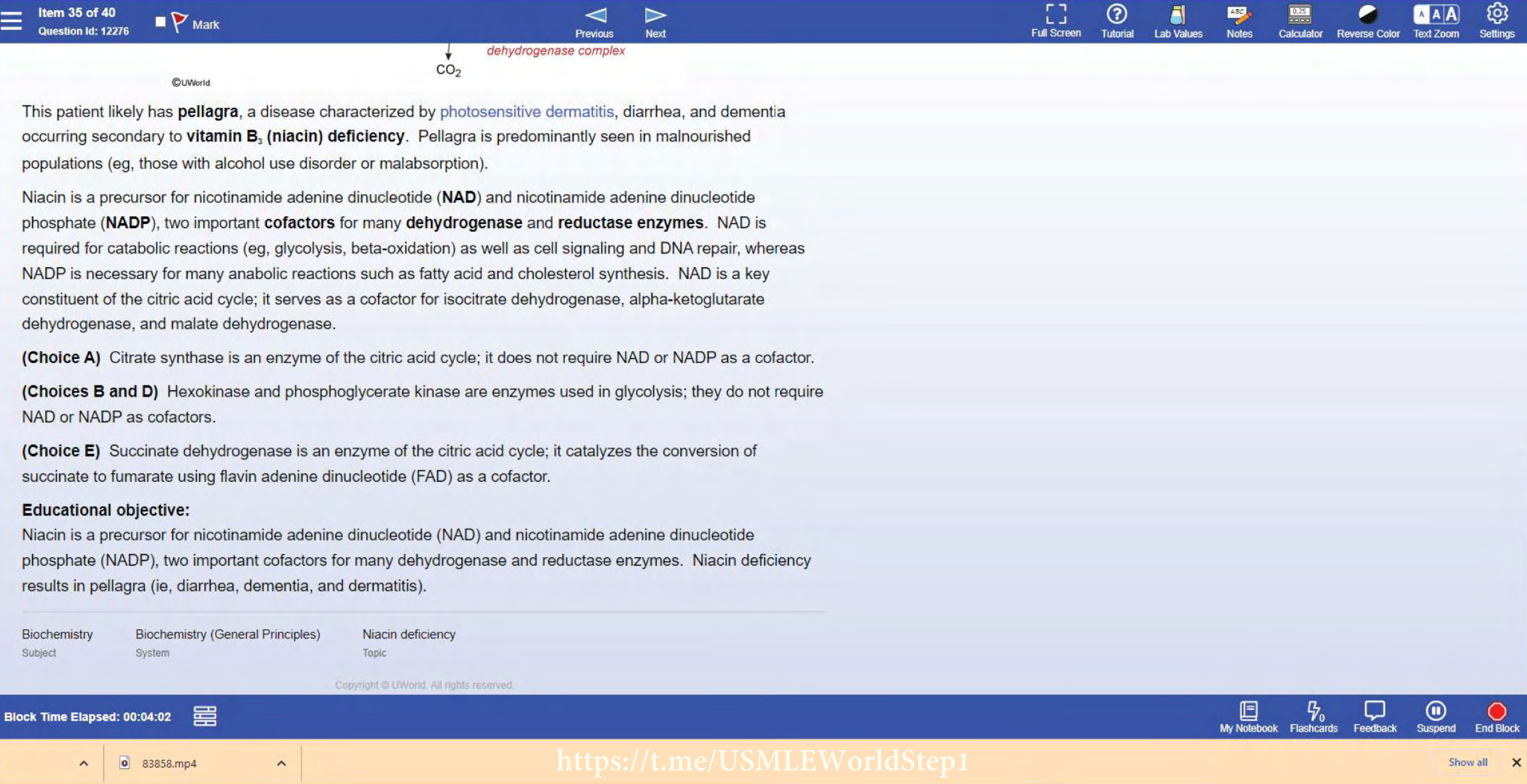
Item 35 of 40
Question Id: 12276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
dehydrogenase complex
CO_2
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This patient likely has **pellagra**, a disease characterized by photosensitive dermatitis, diarrhea, and dementia occurring secondary to **vitamin B_3 (niacin) deficiency**. Pellagra is predominantly seen in malnourished populations (eg, those with alcohol use disorder or malabsorption).

Niacin is a precursor for nicotinamide adenine dinucleotide (**NAD**) and nicotinamide adenine dinucleotide phosphate (**NADP**), two important **cofactors** for many **dehydrogenase** and **reductase enzymes**. NAD is required for catabolic reactions (eg, glycolysis, beta-oxidation) as well as cell signaling and DNA repair, whereas NADP is necessary for many anabolic reactions such as fatty acid and cholesterol synthesis. NAD is a key constituent of the citric acid cycle; it serves as a cofactor for isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase.

(Choice A) Citrate synthase is an enzyme of the citric acid cycle; it does not require NAD or NADP as a cofactor.

(Choices B and D) Hexokinase and phosphoglycerate kinase are enzymes used in glycolysis; they do not require NAD or NADP as cofactors.

(Choice E) Succinate dehydrogenase is an enzyme of the citric acid cycle; it catalyzes the conversion of succinate to fumarate using flavin adenine dinucleotide (FAD) as a cofactor.

Educational objective:

Niacin is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two important cofactors for many dehydrogenase and reductase enzymes. Niacin deficiency results in pellagra (ie, diarrhea, dementia, and dermatitis).

Biochemistry	Biochemistry (General Principles)	Niacin deficiency
Subject	System	Topic

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My Notebook
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Feedback
Suspend
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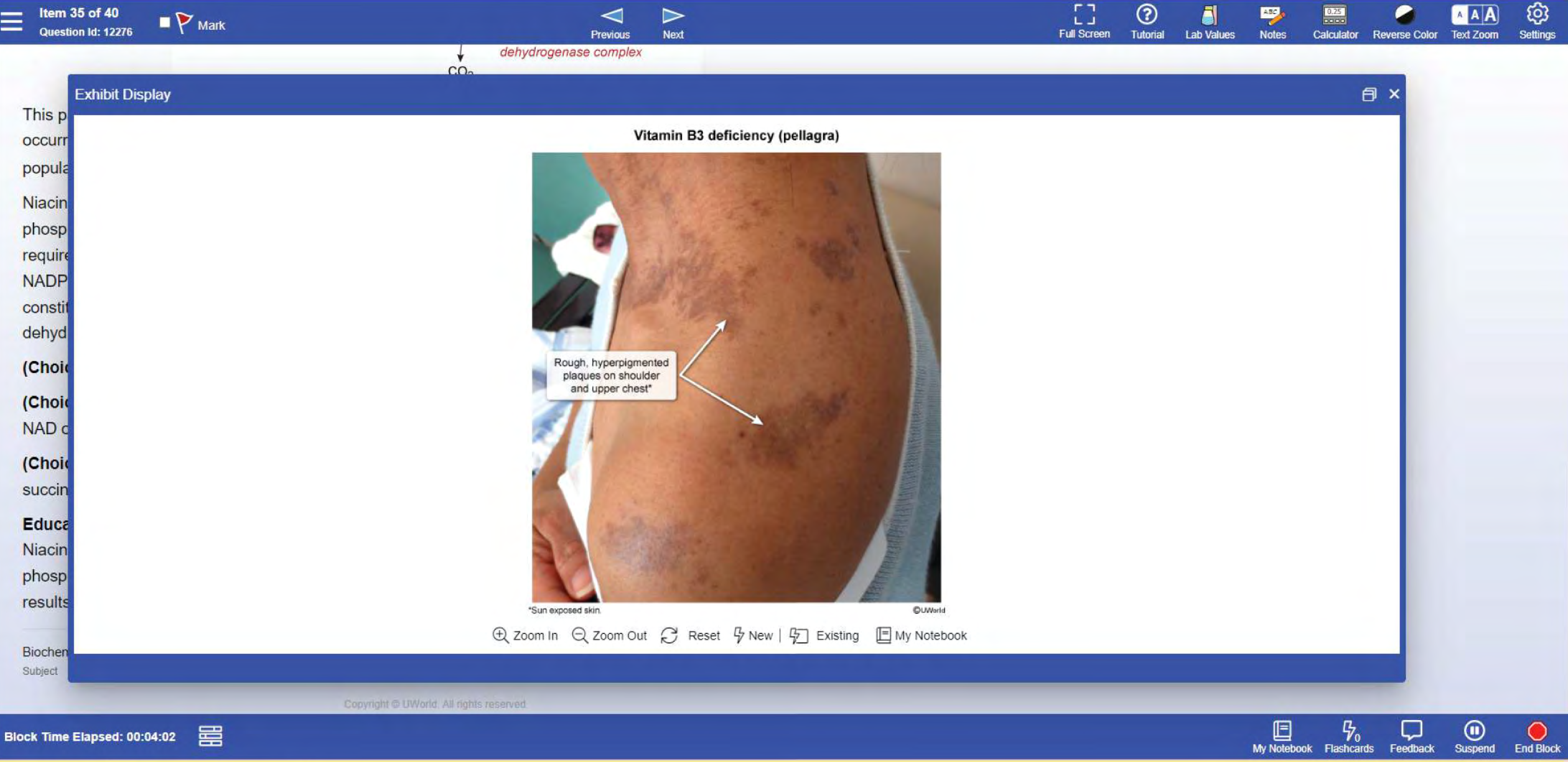
Item 35 of 40
Question Id: 12276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:04:02
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

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Subject

Vitamin B3 deficiency (pellagra)

Rough, hyperpigmented plaques on shoulder and upper chest*

*Sun exposed skin.

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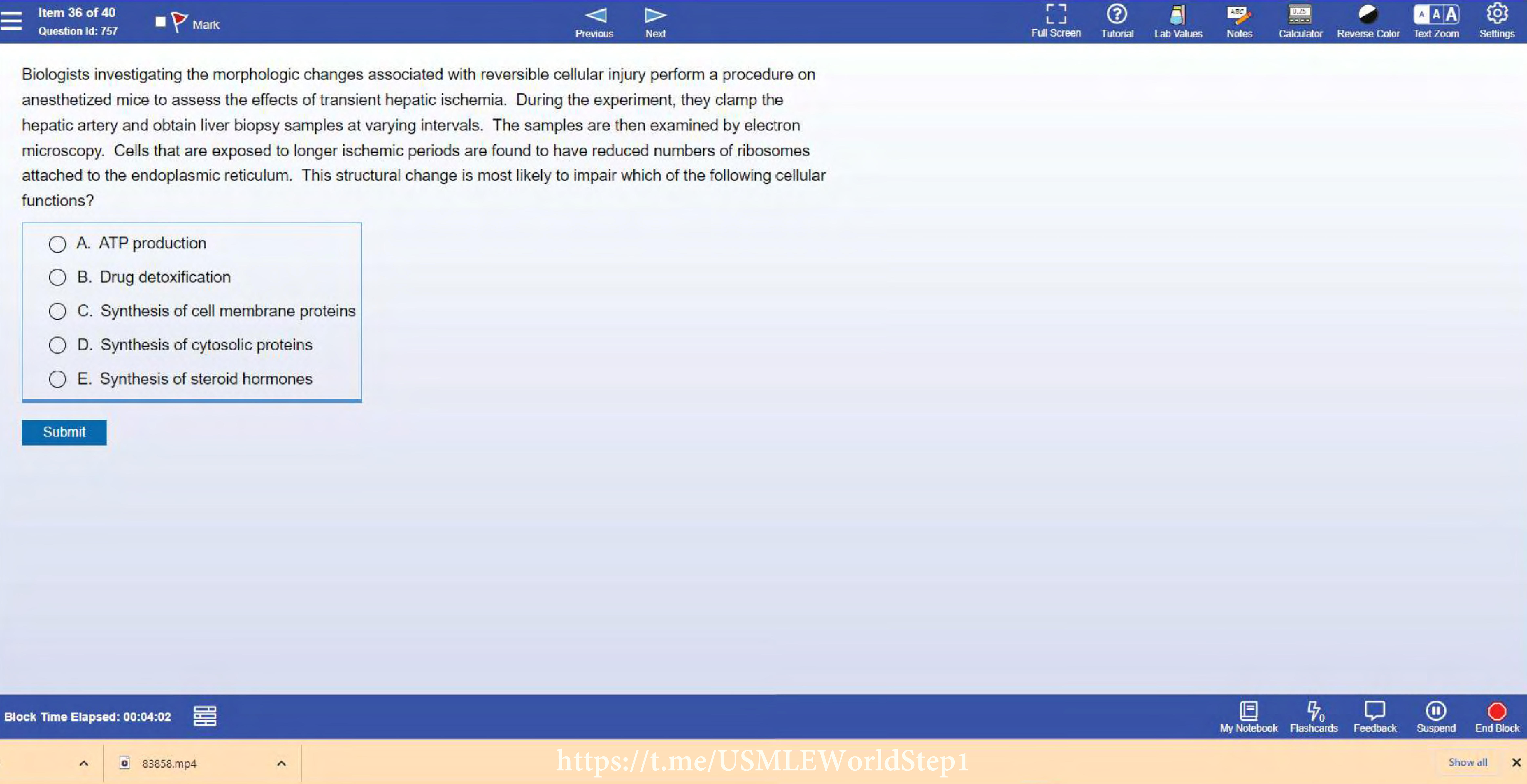
Item 36 of 40
Question Id: 757
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:02
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Biologists investigating the morphologic changes associated with reversible cellular injury perform a procedure on anesthetized mice to assess the effects of transient hepatic ischemia. During the experiment, they clamp the hepatic artery and obtain liver biopsy samples at varying intervals. The samples are then examined by electron microscopy. Cells that are exposed to longer ischemic periods are found to have reduced numbers of ribosomes attached to the endoplasmic reticulum. This structural change is most likely to impair which of the following cellular functions?

○ A. ATP production
○ B. Drug detoxification
○ C. Synthesis of cell membrane proteins
○ D. Synthesis of cytosolic proteins
○ E. Synthesis of steroid hormones

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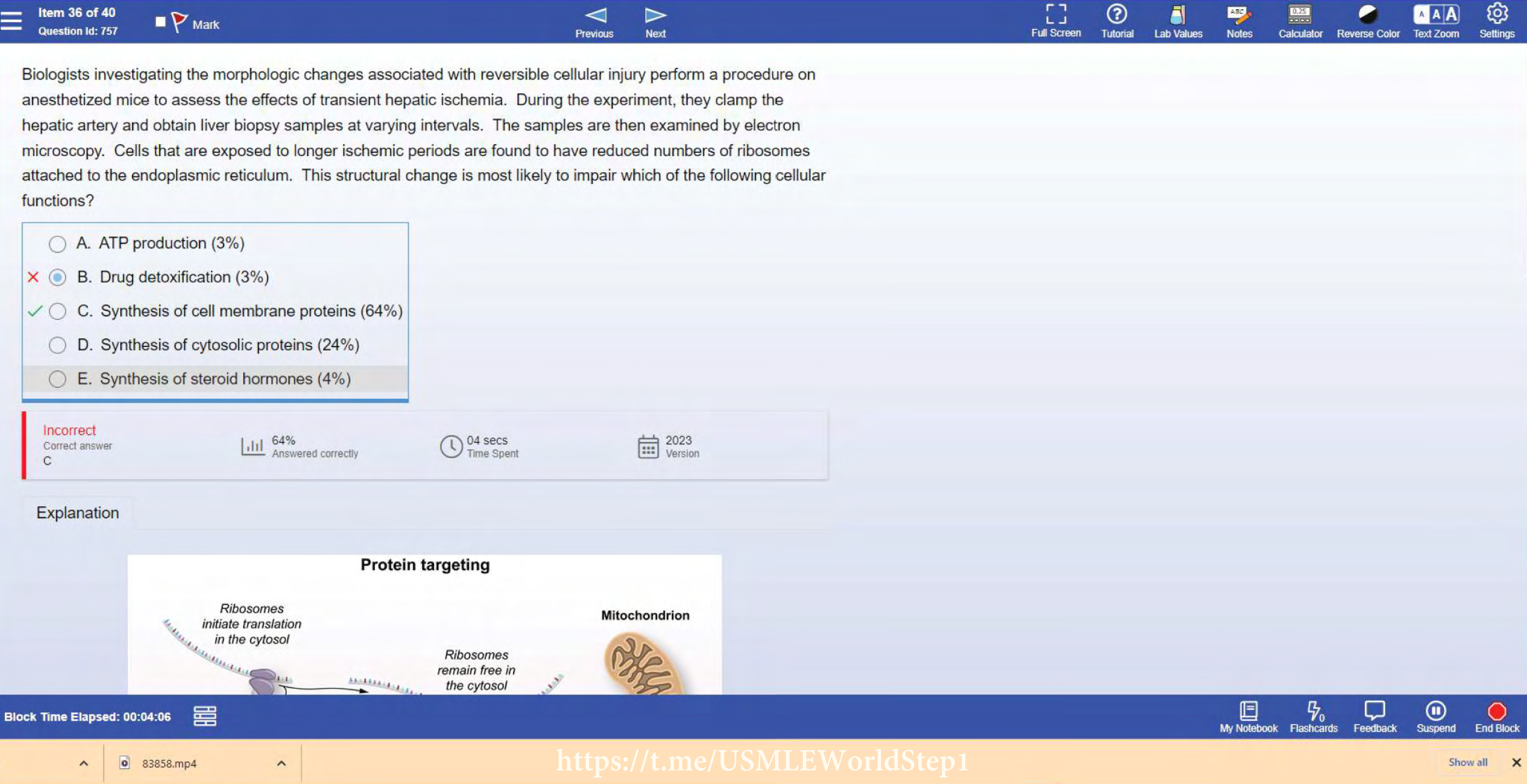

Item 36 of 40
Question Id: 757
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Biologists investigating the morphologic changes associated with reversible cellular injury perform a procedure on anesthetized mice to assess the effects of transient hepatic ischemia. During the experiment, they clamp the hepatic artery and obtain liver biopsy samples at varying intervals. The samples are then examined by electron microscopy. Cells that are exposed to longer ischemic periods are found to have reduced numbers of ribosomes attached to the endoplasmic reticulum. This structural change is most likely to impair which of the following cellular functions?

- ○ A. ATP production (3%)
- ✗ ● B. Drug detoxification (3%)
- ✓ ○ C. Synthesis of cell membrane proteins (64%)
- ○ D. Synthesis of cytosolic proteins (24%)
- ○ E. Synthesis of steroid hormones (4%)

Incorrect
Correct answer
C

64%
Answered correctly

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2023
Version

Explanation

Protein targeting

Ribosomes initiate translation in the cytosol
Ribosomes remain free in the cytosol
Mitochondrion

Block Time Elapsed: 00:04:06
My Notebook
Flashcards
Feedback
Suspend
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Show all

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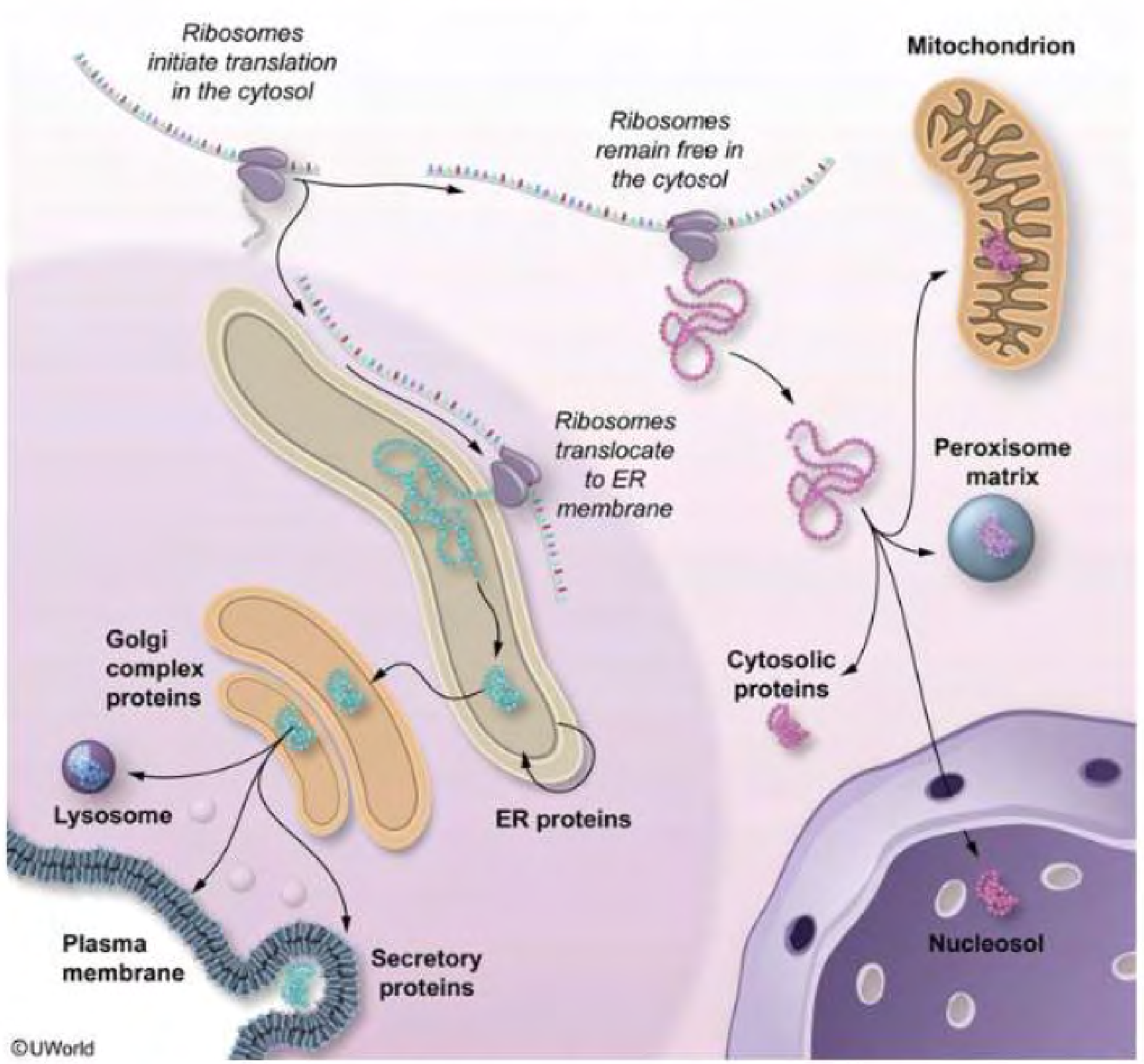
Protein targeting


Ribosomes initiate translation in the cytosol
Ribosomes remain free in the cytosol
Mitochondrion
Ribosomes translocate to ER membrane
Peroxisome matrix
Golgi complex proteins
Cytosolic proteins
Lysosome
ER proteins
Plasma membrane
Secretory proteins
Nucleosol
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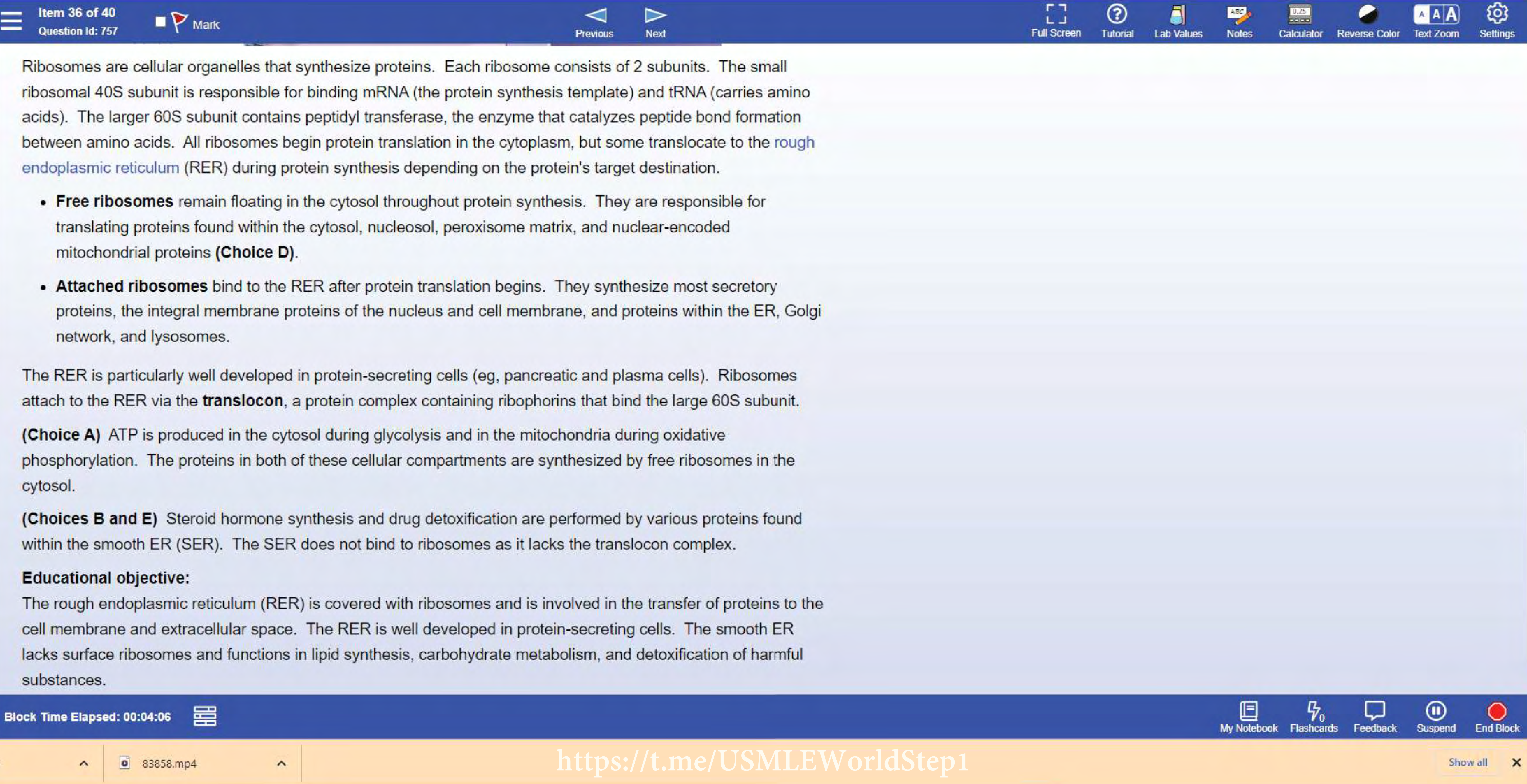
membrane
Secretory proteins



Ribosomes are cellular organelles that synthesize proteins. Each ribosome consists of 2 subunits. The small ribosomal 40S subunit is responsible for binding mRNA (the protein synthesis template) and tRNA (carries amino acids). The larger 60S subunit contains peptidyl transferase, the enzyme that catalyzes peptide bond formation between amino acids. All ribosomes begin protein translation in the cytoplasm, but some translocate to the rough endoplasmic reticulum (RER) during protein synthesis depending on the protein's target destination.

- **Free ribosomes** remain floating in the cytosol throughout protein synthesis. They are responsible for translating proteins found within the cytosol, nucleosol, peroxisome matrix, and nuclear-encoded mitochondrial proteins **(Choice D)**.
- **Attached ribosomes** bind to the RER after protein translation begins. They synthesize most secretory proteins, the integral membrane proteins of the nucleus and cell membrane, and proteins within the ER, Golgi network, and lysosomes.

The RER is particularly well developed in protein-secreting cells (eg, pancreatic and plasma cells). Ribosomes attach to the RER via the **translocon**, a protein complex containing ribophorins that bind the large 60S subunit.

(Choice A) ATP is produced in the cytosol during glycolysis and in the mitochondria during oxidative phosphorylation. The proteins in both of these cellular compartments are synthesized by free ribosomes in the cytosol.

(Choices B and E) Steroid hormone synthesis and drug detoxification are performed by various proteins found within the smooth ER (SER). The SER does not bind to ribosomes as it lacks the translocon complex.

Educational objective:

The rough endoplasmic reticulum (RER) is covered with ribosomes and is involved in the transfer of proteins to the cell membrane and extracellular space. The RER is well developed in protein-secreting cells. The smooth ER lacks surface ribosomes and functions in lipid synthesis, carbohydrate metabolism, and detoxification of harmful substances.

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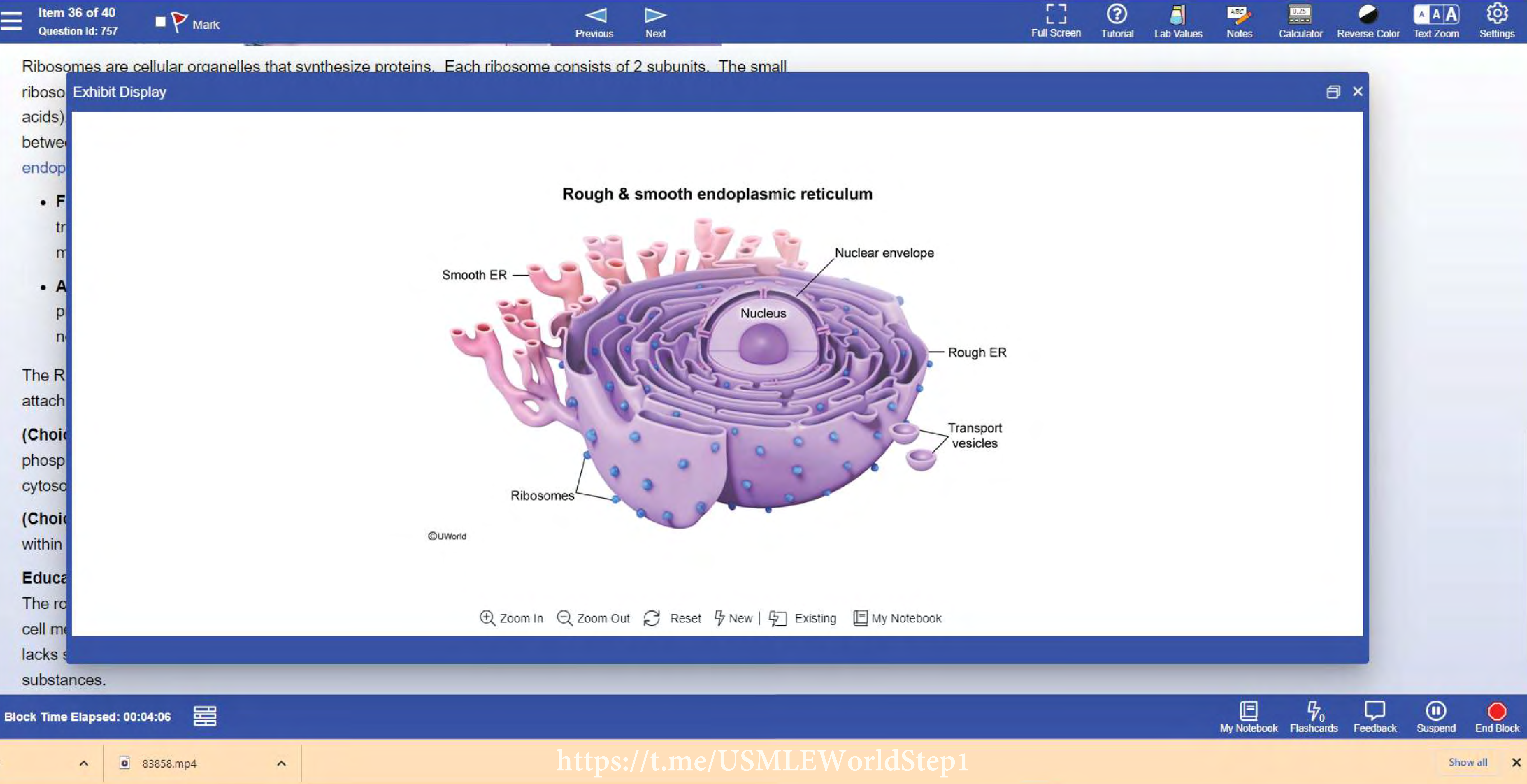
Item 36 of 40
Question Id: 757
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Ribosomes are cellular organelles that synthesize proteins. Each ribosome consists of 2 subunits. The small

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Rough & smooth endoplasmic reticulum

Smooth ER
Nuclear envelope
Nucleus
Rough ER
Transport vesicles
Ribosomes

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My Notebook

Block Time Elapsed: 00:04:06

My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
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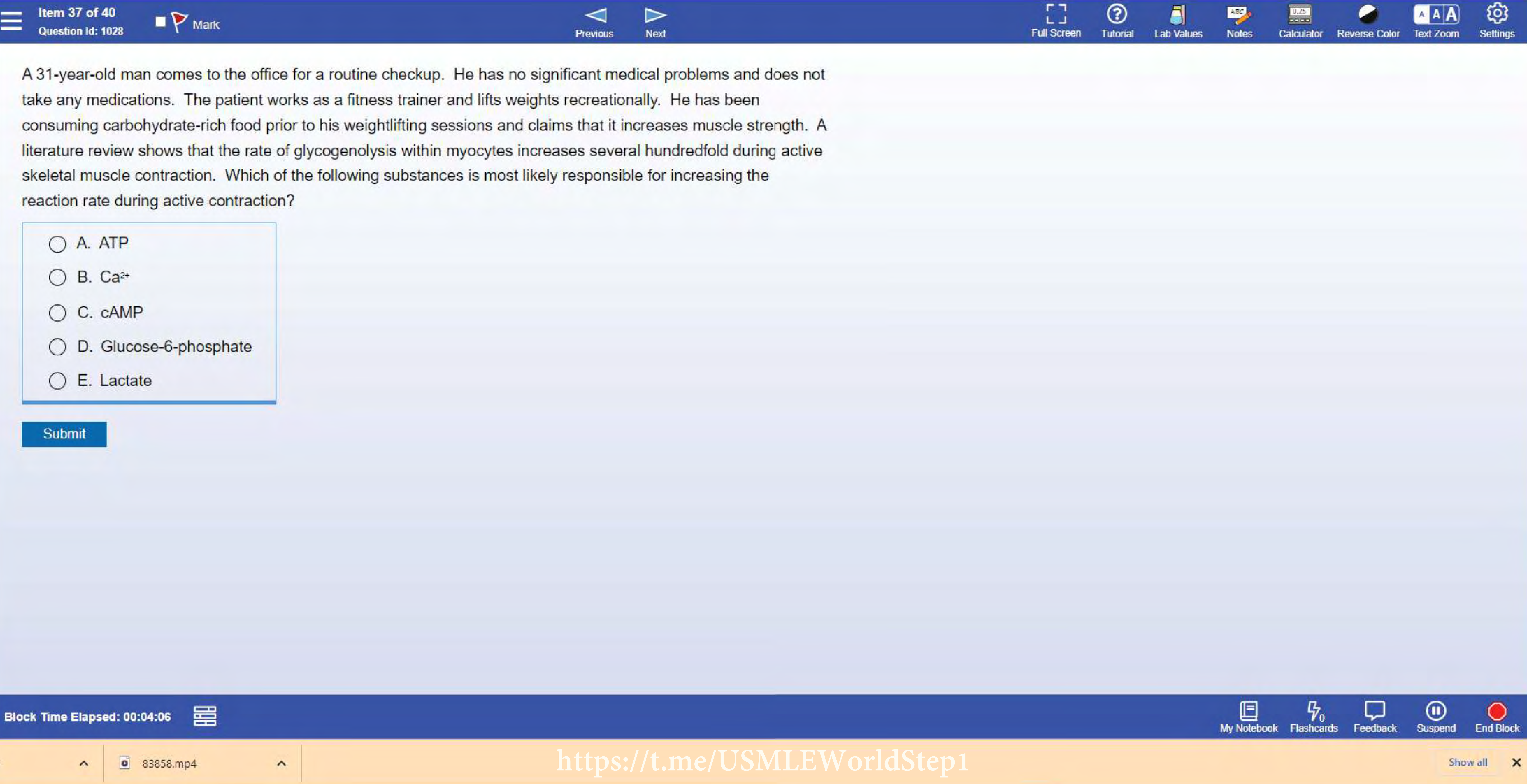
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Item 37 of 40
Question Id: 1028

A 31-year-old man comes to the office for a routine checkup. He has no significant medical problems and does not take any medications. The patient works as a fitness trainer and lifts weights recreationally. He has been consuming carbohydrate-rich food prior to his weightlifting sessions and claims that it increases muscle strength. A literature review shows that the rate of glycogenolysis within myocytes increases several hundredfold during active skeletal muscle contraction. Which of the following substances is most likely responsible for increasing the reaction rate during active contraction?

○ A. ATP
○ B. Ca^{2+}
○ C. cAMP
○ D. Glucose-6-phosphate
○ E. Lactate

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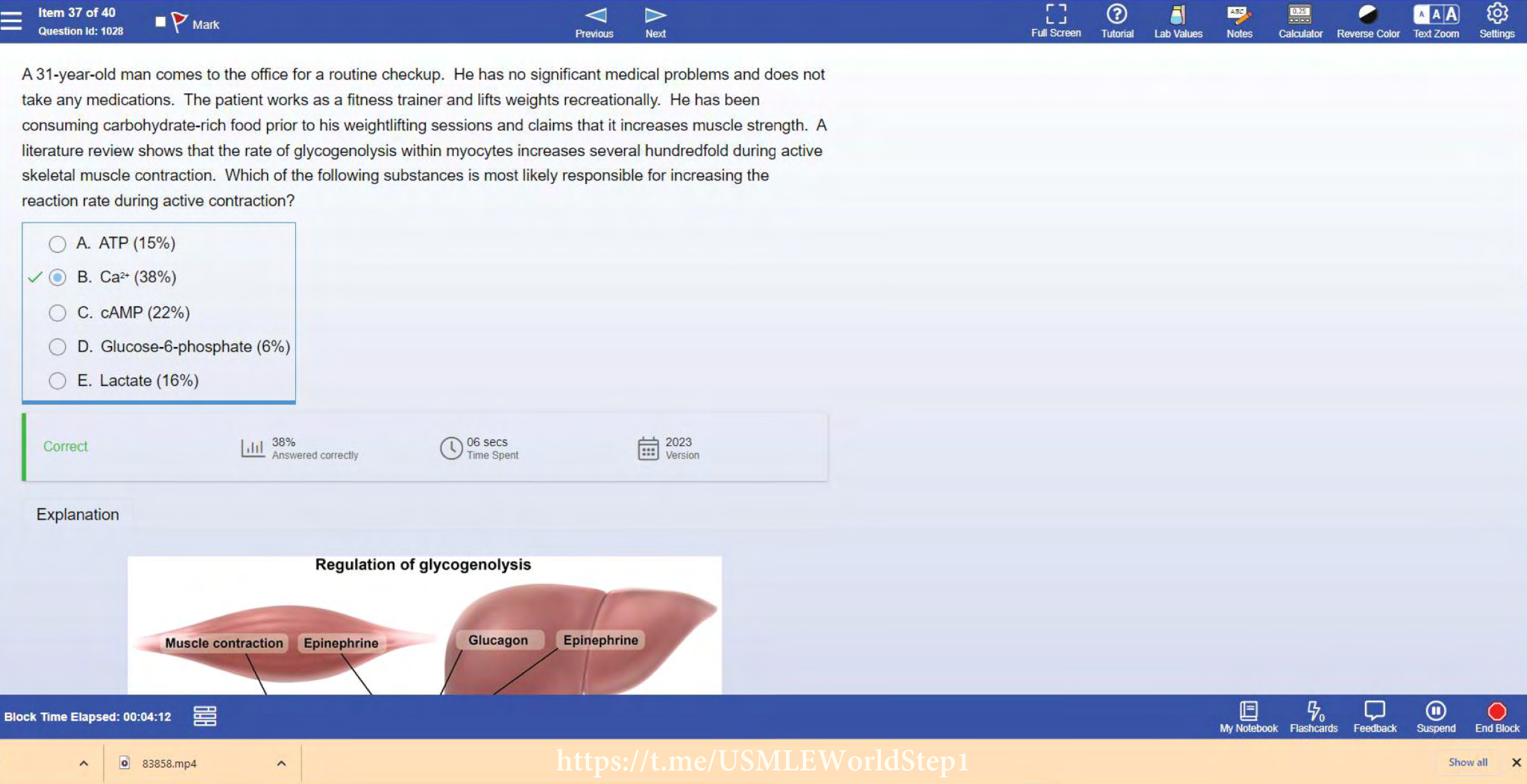

Item 37 of 40
Question Id: 1028
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ A. ATP (15%)
- ✓ ● B. Ca^{2+} (38%)
- ○ C. cAMP (22%)
- ○ D. Glucose-6-phosphate (6%)
- ○ E. Lactate (16%)

Correct

38%
Answered correctly

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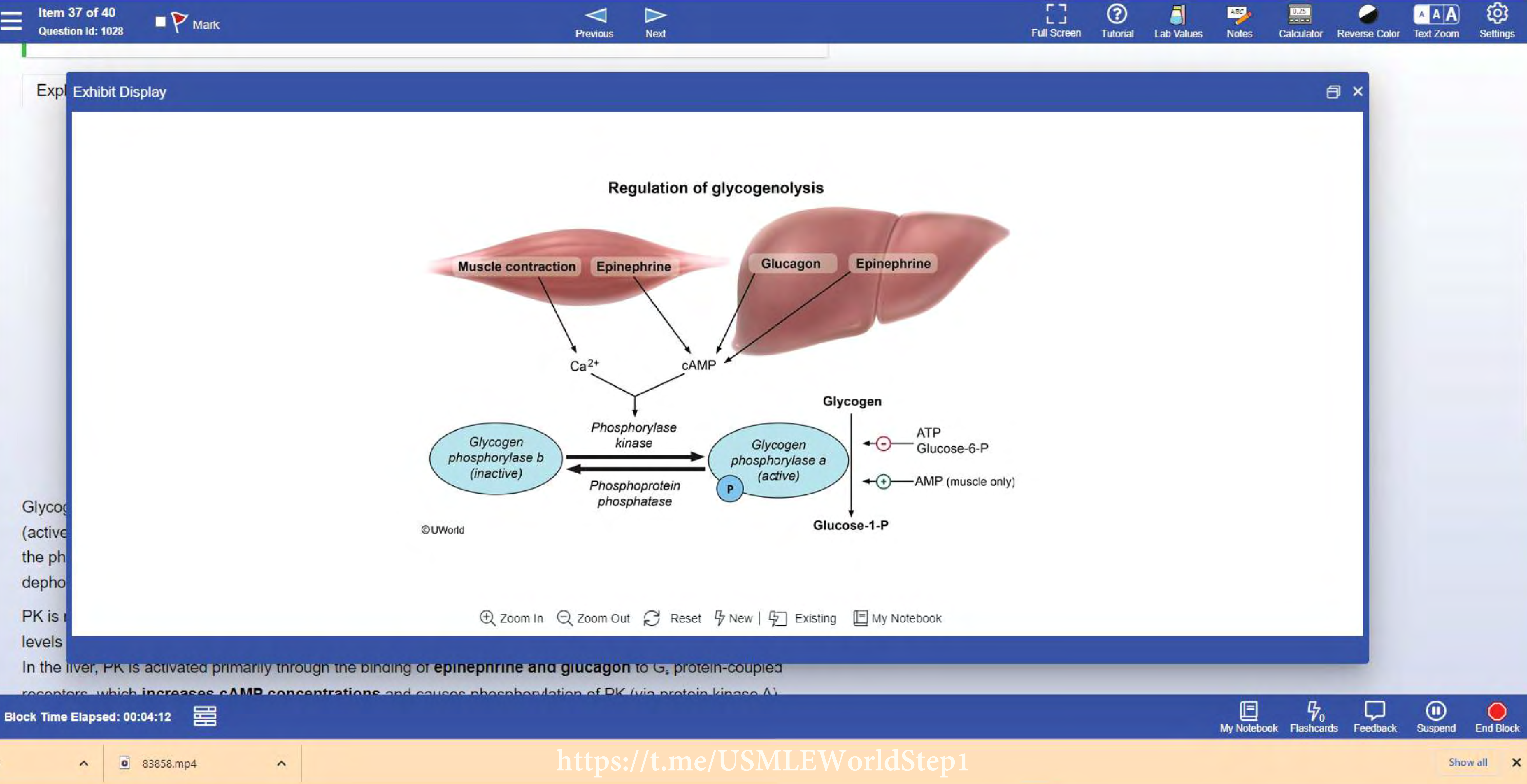
2023
Version

Explanation

Regulation of glycogenolysis

Muscle contraction
Epinephrine
Glucagon
Epinephrine
Block Time Elapsed: 00:04:12
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all



Item 37 of 40
Question Id: 1028

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Regulation of glycogenolysis
Muscle contraction
Epinephrine
Glucagon
Epinephrine
Ca^{2+}
cAMP
Glycogen phosphorylase b (inactive)
Phosphorylase kinase
Phosphoprotein phosphatase
Glycogen phosphorylase a (active)
P
Glycogen
ATP
Glucose-6-P
AMP (muscle only)
Glucose-1-P
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New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block
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Glycog

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PK is

levels

In the liver, PK is activated primarily through the binding of **epinephrine and glucagon** to G_s protein-coupled receptors, which **increases cAMP concentrations** and causes phosphorylation of PK (via protein kinase A).

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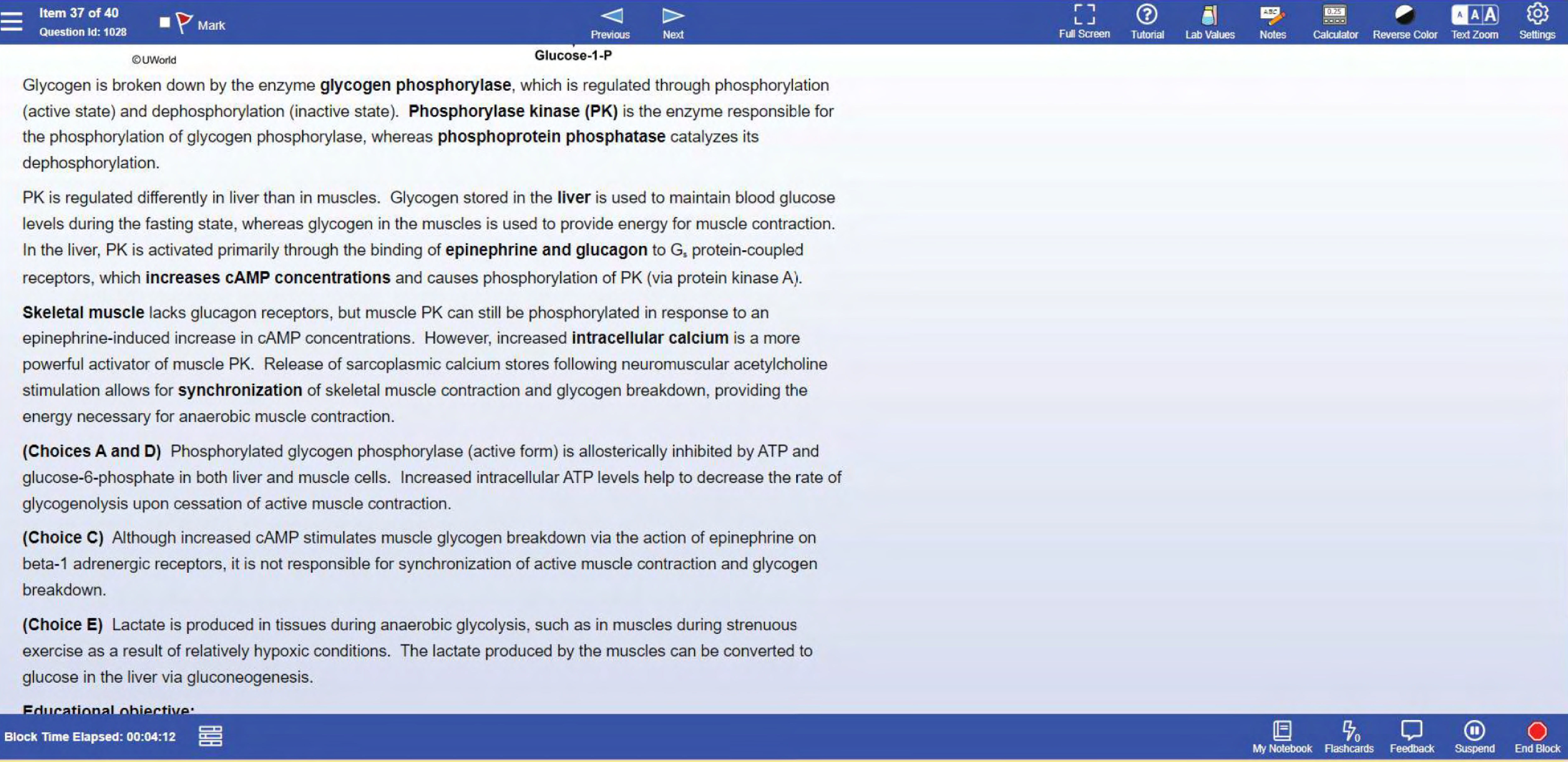

Glycogen is broken down by the enzyme **glycogen phosphorylase**, which is regulated through phosphorylation (active state) and dephosphorylation (inactive state). **Phosphorylase kinase (PK)** is the enzyme responsible for the phosphorylation of glycogen phosphorylase, whereas **phosphoprotein phosphatase** catalyzes its dephosphorylation.

PK is regulated differently in liver than in muscles. Glycogen stored in the **liver** is used to maintain blood glucose levels during the fasting state, whereas glycogen in the muscles is used to provide energy for muscle contraction. In the liver, PK is activated primarily through the binding of **epinephrine and glucagon** to G_s protein-coupled receptors, which **increases cAMP concentrations** and causes phosphorylation of PK (via protein kinase A).

Skeletal muscle lacks glucagon receptors, but muscle PK can still be phosphorylated in response to an epinephrine-induced increase in cAMP concentrations. However, increased **intracellular calcium** is a more powerful activator of muscle PK. Release of sarcoplasmic calcium stores following neuromuscular acetylcholine stimulation allows for **synchronization** of skeletal muscle contraction and glycogen breakdown, providing the energy necessary for anaerobic muscle contraction.

(Choices A and D) Phosphorylated glycogen phosphorylase (active form) is allosterically inhibited by ATP and glucose-6-phosphate in both liver and muscle cells. Increased intracellular ATP levels help to decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle contraction and glycogen breakdown.

(Choice E) Lactate is produced in tissues during anaerobic glycolysis, such as in muscles during strenuous exercise as a result of relatively hypoxic conditions. The lactate produced by the muscles can be converted to glucose in the liver via gluconeogenesis.

Educational objective:

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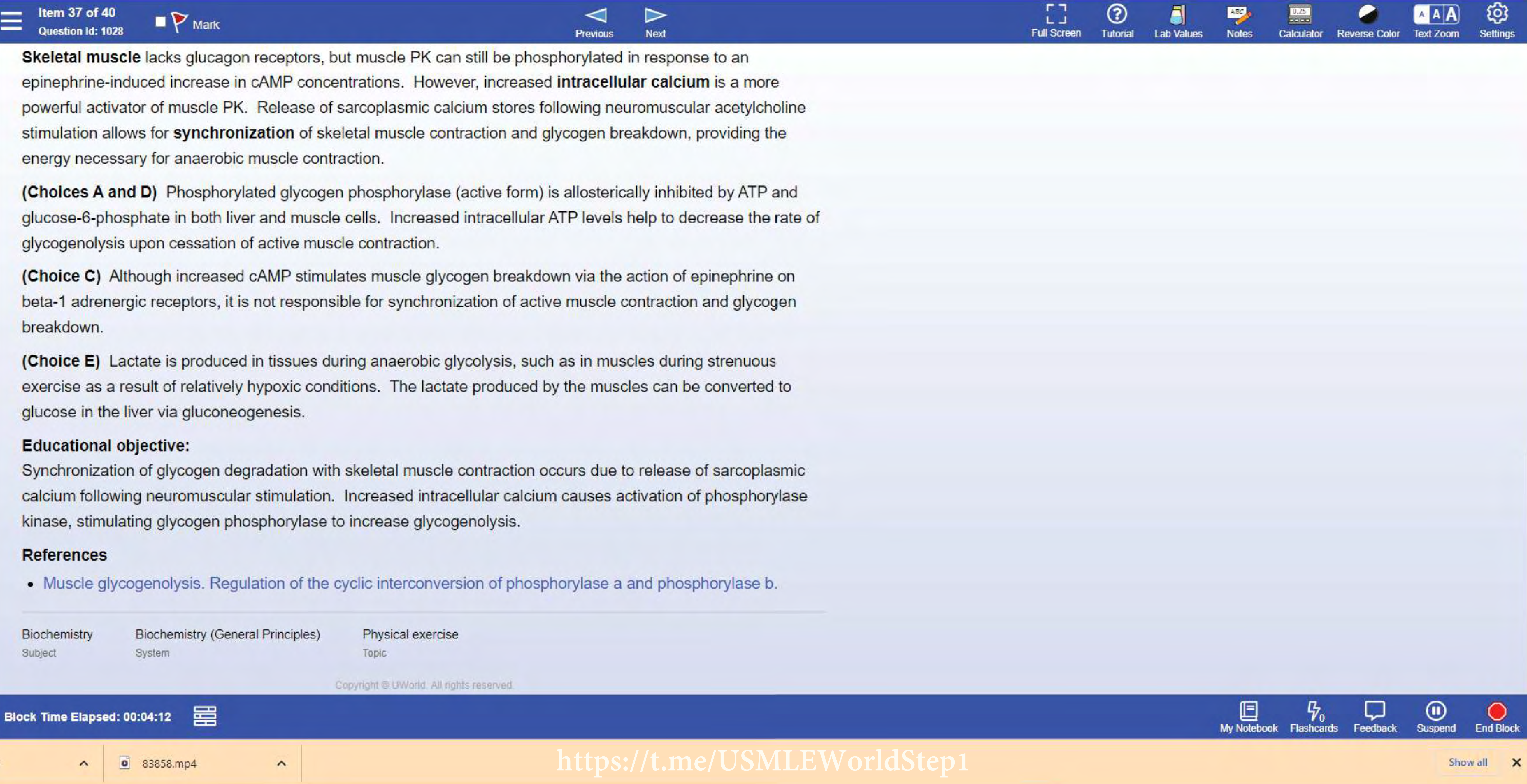
Item 37 of 40
Question Id: 1028
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choices A and D) Phosphorylated glycogen phosphorylase (active form) is allosterically inhibited by ATP and glucose-6-phosphate in both liver and muscle cells. Increased intracellular ATP levels help to decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle contraction and glycogen breakdown.

(Choice E) Lactate is produced in tissues during anaerobic glycolysis, such as in muscles during strenuous exercise as a result of relatively hypoxic conditions. The lactate produced by the muscles can be converted to glucose in the liver via gluconeogenesis.

Educational objective:

Synchronization of glycogen degradation with skeletal muscle contraction occurs due to release of sarcoplasmic calcium following neuromuscular stimulation. Increased intracellular calcium causes activation of phosphorylase kinase, stimulating glycogen phosphorylase to increase glycogenolysis.

References

- Muscle glycogenolysis. Regulation of the cyclic interconversion of phosphorylase a and phosphorylase b.

Biochemistry	Biochemistry (General Principles)	Physical exercise
Subject	System	Topic

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My Notebook
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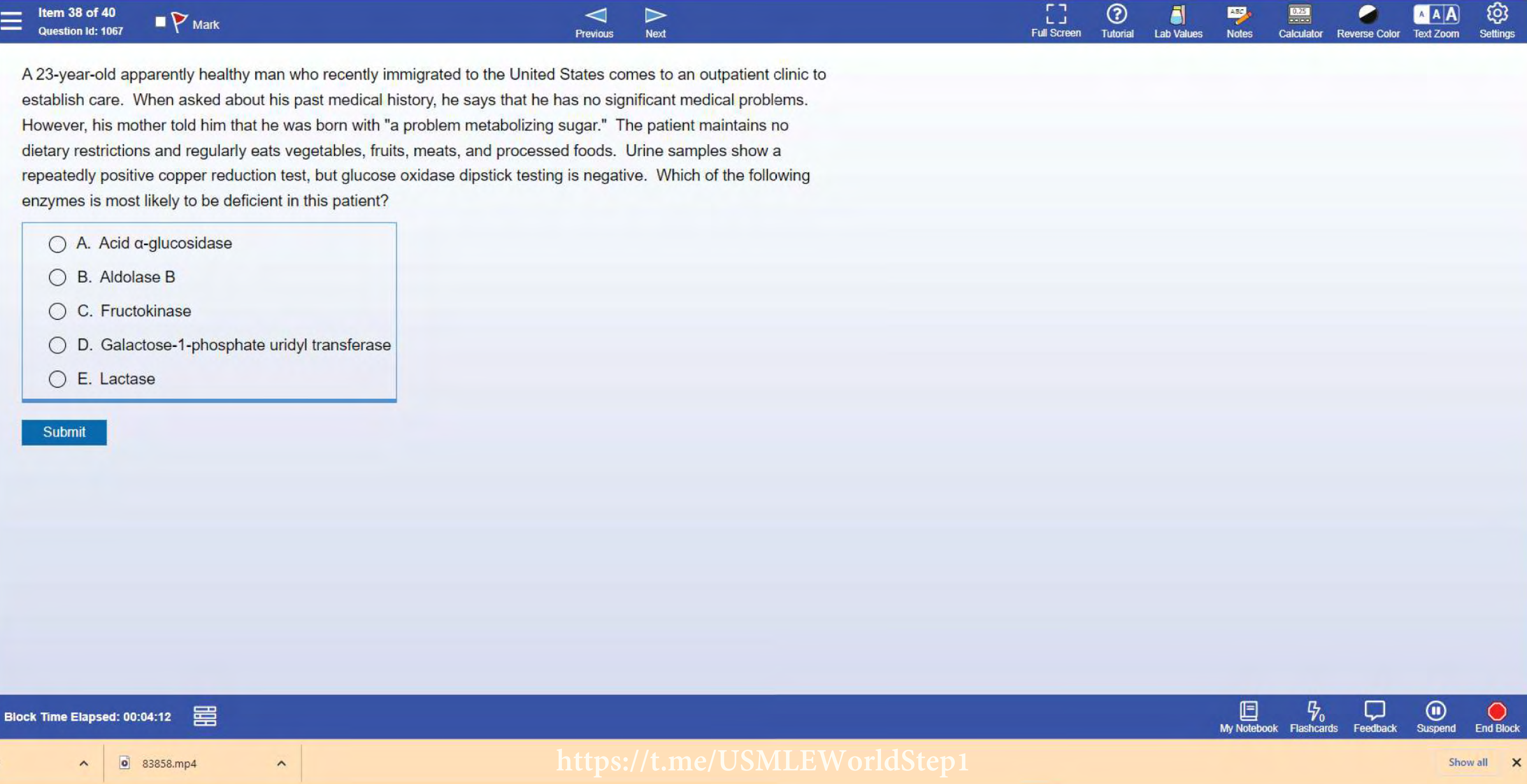
Item 38 of 40
Question Id: 1067
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Block Time Elapsed: 00:04:12
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Flashcards
Feedback
Suspend
End Block
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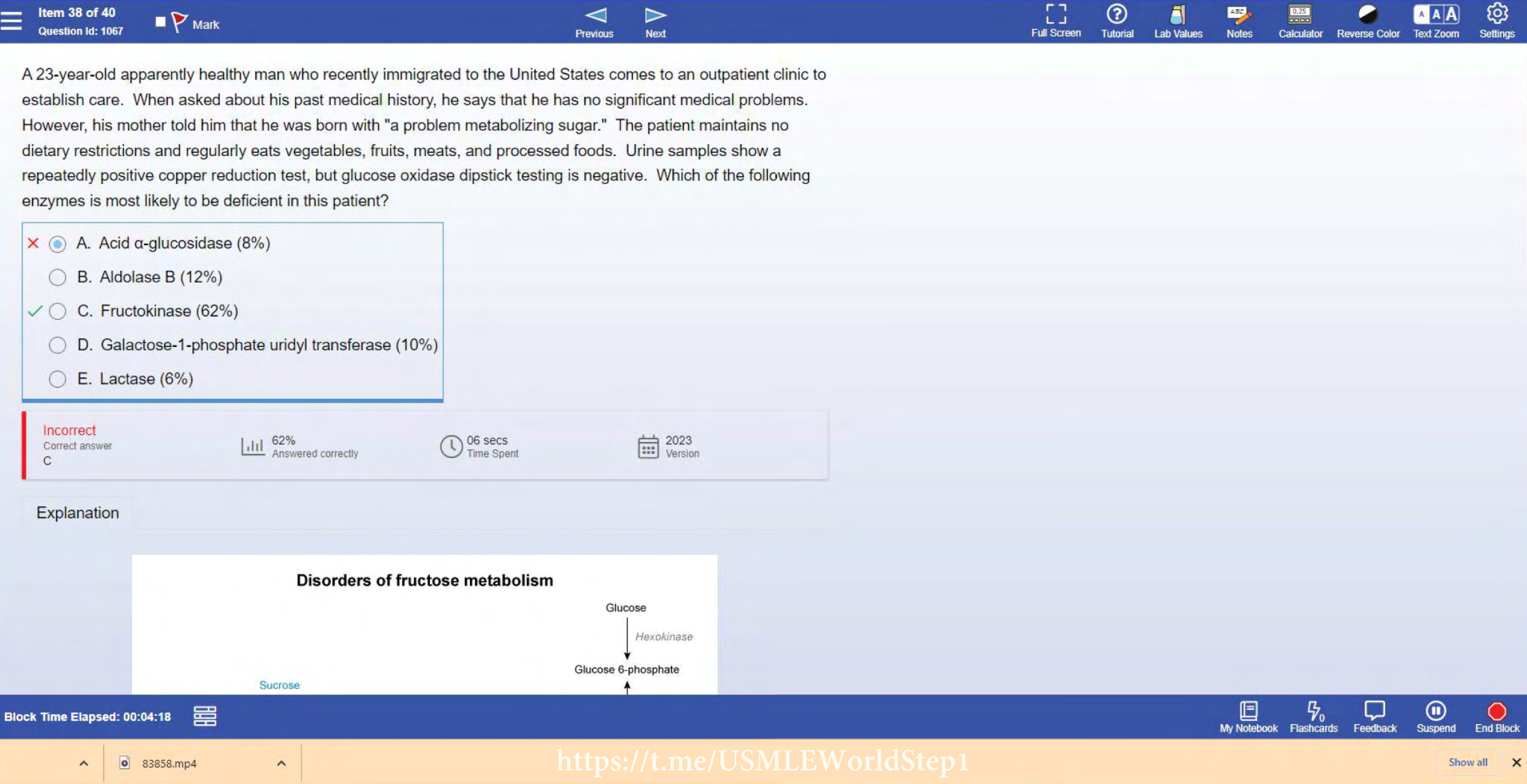
A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

○ A. Acid α-glucosidase
○ B. Aldolase B
○ C. Fructokinase
○ D. Galactose-1-phosphate uridyl transferase
○ E. Lactase


Item 38 of 40
Question Id: 1067
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

- ✗ ● A. Acid α-glucosidase (8%)
- ○ B. Aldolase B (12%)
- ✓ ○ C. Fructokinase (62%)
- ○ D. Galactose-1-phosphate uridyl transferase (10%)
- ○ E. Lactase (6%)

Incorrect
Correct answer
C

62%
Answered correctly

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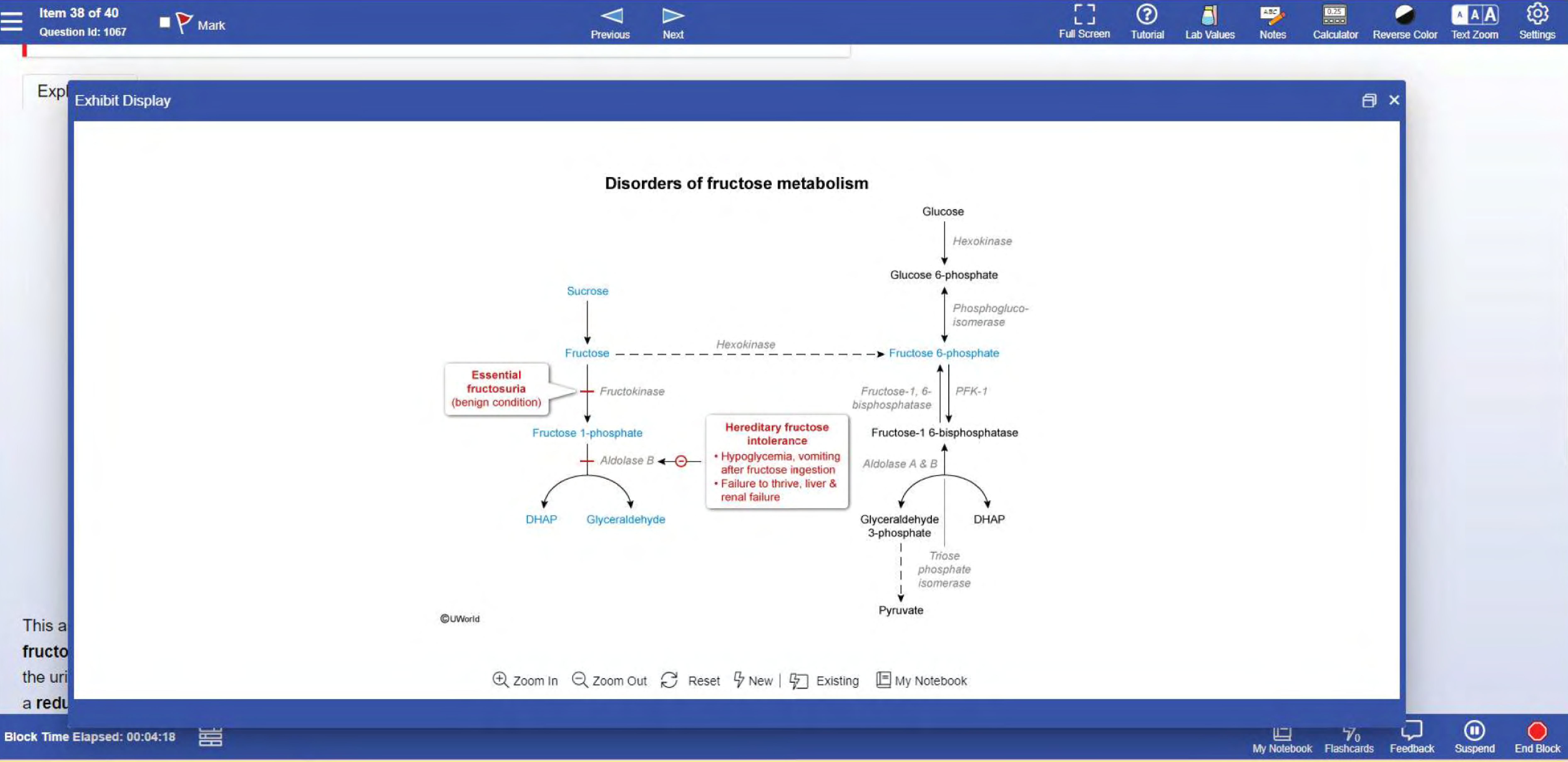
Explanation

Disorders of fructose metabolism

Glucose
Hexokinase
Glucose 6-phosphate
Sucrose


Item 38 of 40
Question Id: 1067
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Disorders of fructose metabolism
Glucose
Hexokinase
Glucose 6-phosphate
Phosphogluco-isomerase
Sucrose
Fructose
Hexokinase
Fructose 6-phosphate
Essential fructosuria (benign condition)
Fructokinase
Fructose-1, 6-bisphosphatase
PFK-1
Fructose 1-phosphate
Fructose-1 6-bisphosphatase
Aldolase B
Hereditary fructose intolerance
• Hypoglycemia, vomiting after fructose ingestion
• Failure to thrive, liver & renal failure
Aldolase A & B
DHAP
Glyceraldehyde
Glyceraldehyde 3-phosphate
DHAP
Triose phosphate isomerase
Pyruvate
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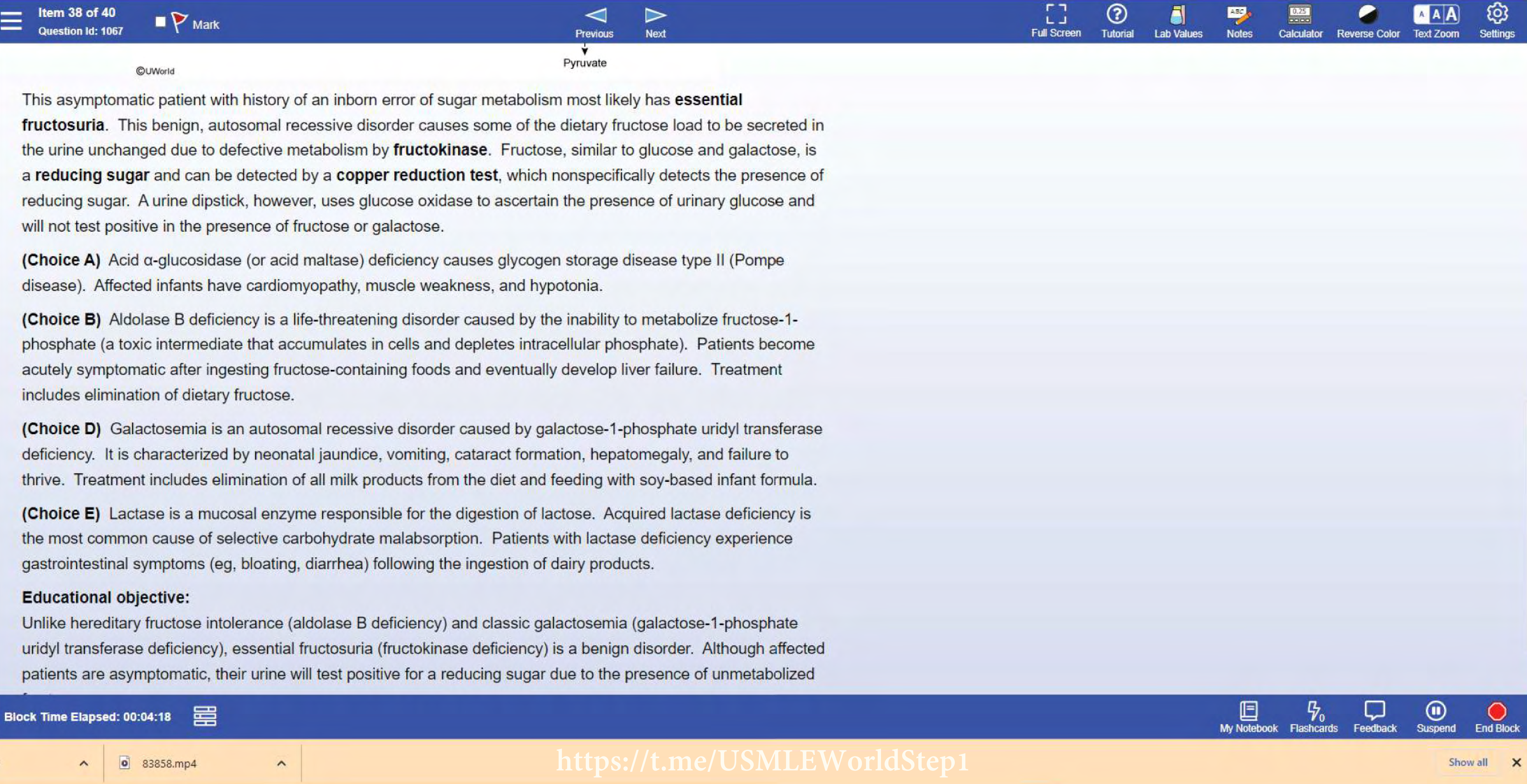


This asymptomatic patient with history of an inborn error of sugar metabolism most likely has **essential fructosuria**. This benign, autosomal recessive disorder causes some of the dietary fructose load to be secreted in the urine unchanged due to defective metabolism by **fructokinase**. Fructose, similar to glucose and galactose, is a **reducing sugar** and can be detected by a **copper reduction test**, which nonspecifically detects the presence of reducing sugar. A urine dipstick, however, uses glucose oxidase to ascertain the presence of urinary glucose and will not test positive in the presence of fructose or galactose.

(Choice A) Acid α-glucosidase (or acid maltase) deficiency causes glycogen storage disease type II (Pompe disease). Affected infants have cardiomyopathy, muscle weakness, and hypotonia.

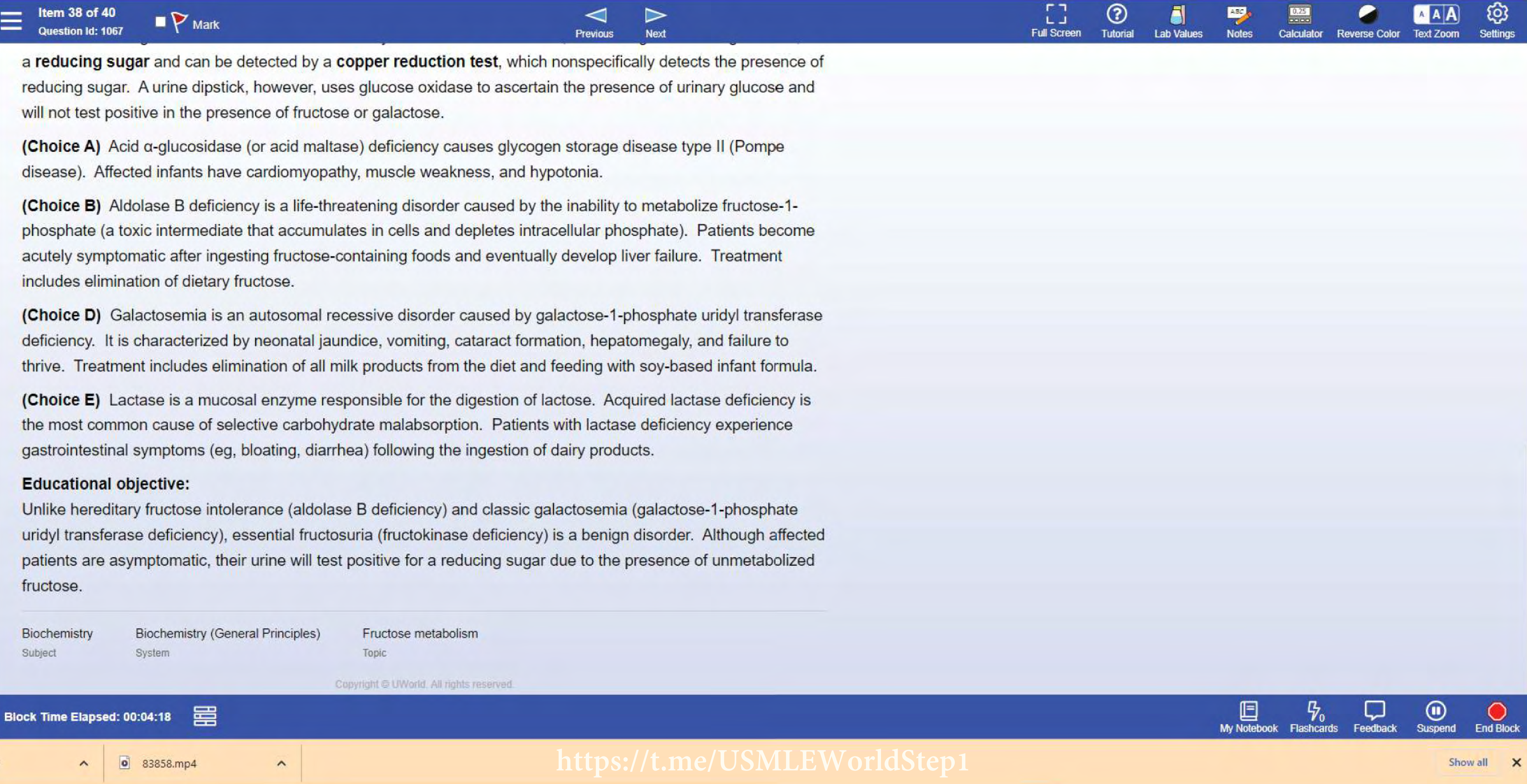
(Choice B) Aldolase B deficiency is a life-threatening disorder caused by the inability to metabolize fructose-1-phosphate (a toxic intermediate that accumulates in cells and depletes intracellular phosphate). Patients become acutely symptomatic after ingesting fructose-containing foods and eventually develop liver failure. Treatment includes elimination of dietary fructose.

(Choice D) Galactosemia is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase deficiency. It is characterized by neonatal jaundice, vomiting, cataract formation, hepatomegaly, and failure to thrive. Treatment includes elimination of all milk products from the diet and feeding with soy-based infant formula.

(Choice E) Lactase is a mucosal enzyme responsible for the digestion of lactose. Acquired lactase deficiency is the most common cause of selective carbohydrate malabsorption. Patients with lactase deficiency experience gastrointestinal symptoms (eg, bloating, diarrhea) following the ingestion of dairy products.

Educational objective:

Unlike hereditary fructose intolerance (aldolase B deficiency) and classic galactosemia (galactose-1-phosphate uridyl transferase deficiency), essential fructosuria (fructokinase deficiency) is a benign disorder. Although affected patients are asymptomatic, their urine will test positive for a reducing sugar due to the presence of unmetabolized


Item 38 of 40
Question Id: 1067
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Educational objective:

Unlike hereditary fructose intolerance (aldolase B deficiency) and classic galactosemia (galactose-1-phosphate uridyl transferase deficiency), essential fructosuria (fructokinase deficiency) is a benign disorder. Although affected patients are asymptomatic, their urine will test positive for a reducing sugar due to the presence of unmetabolized fructose.

Biochemistry	Biochemistry (General Principles)	Fructose metabolism
Subject	System	Topic

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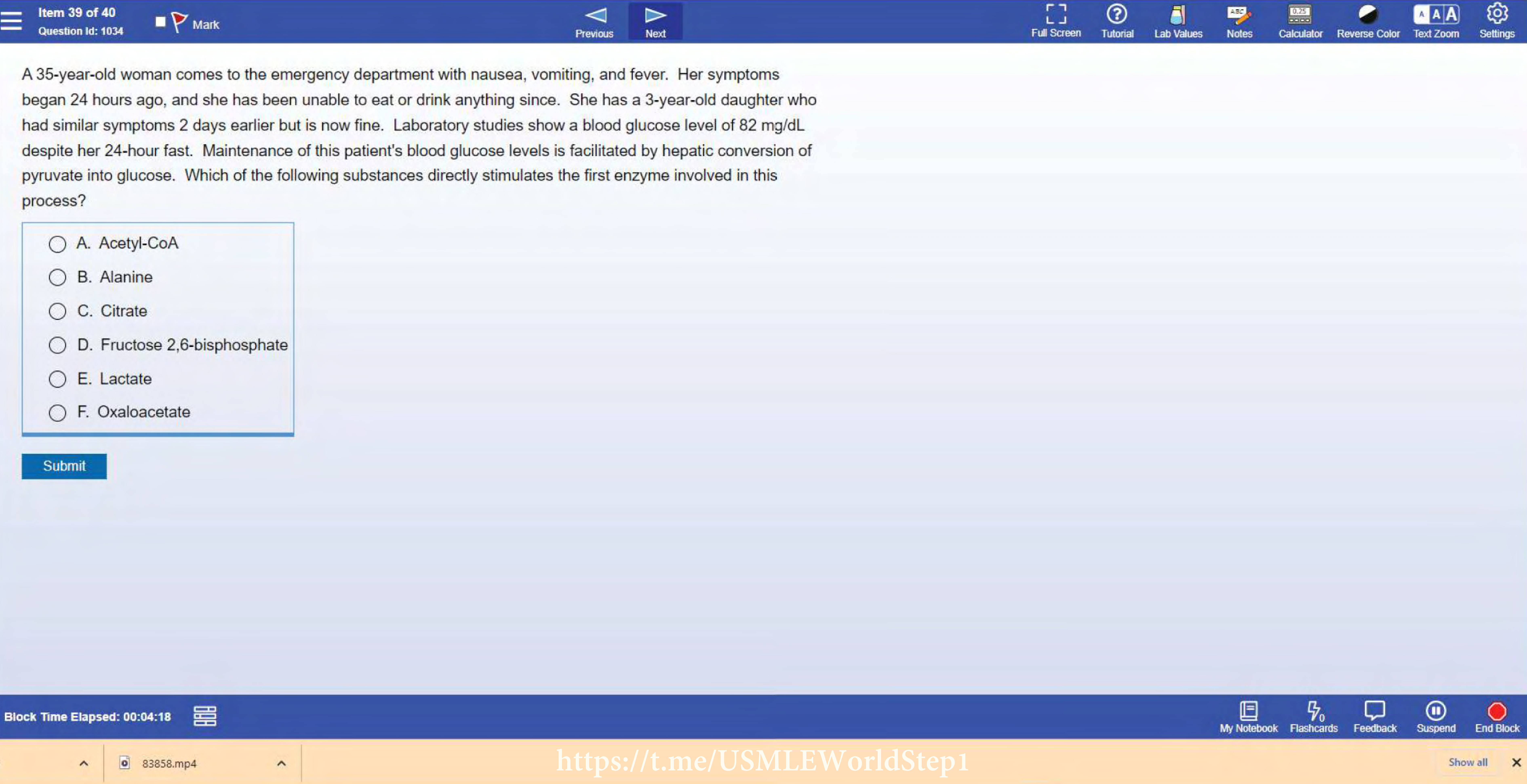
Item 39 of 40
Question Id: 1034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:18
My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

A 35-year-old woman comes to the emergency department with nausea, vomiting, and fever. Her symptoms began 24 hours ago, and she has been unable to eat or drink anything since. She has a 3-year-old daughter who had similar symptoms 2 days earlier but is now fine. Laboratory studies show a blood glucose level of 82 mg/dL despite her 24-hour fast. Maintenance of this patient's blood glucose levels is facilitated by hepatic conversion of pyruvate into glucose. Which of the following substances directly stimulates the first enzyme involved in this process?

○ A. Acetyl-CoA
○ B. Alanine
○ C. Citrate
○ D. Fructose 2,6-bisphosphate
○ E. Lactate
○ F. Oxaloacetate

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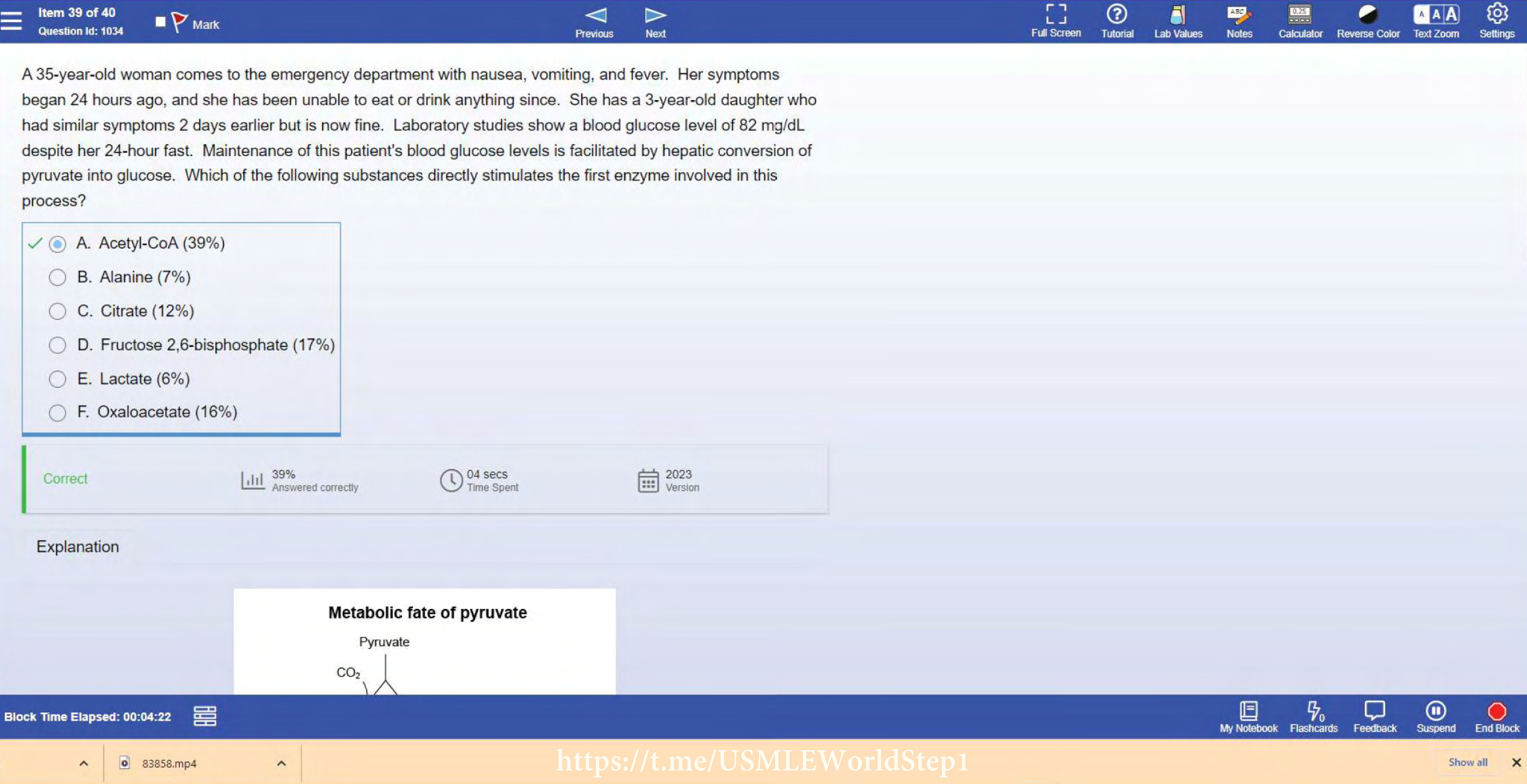
Item 39 of 40
Question Id: 1034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:22
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Feedback
Suspend
End Block
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A 35-year-old woman comes to the emergency department with nausea, vomiting, and fever. Her symptoms began 24 hours ago, and she has been unable to eat or drink anything since. She has a 3-year-old daughter who had similar symptoms 2 days earlier but is now fine. Laboratory studies show a blood glucose level of 82 mg/dL despite her 24-hour fast. Maintenance of this patient's blood glucose levels is facilitated by hepatic conversion of pyruvate into glucose. Which of the following substances directly stimulates the first enzyme involved in this process?

- ✓ ● A. Acetyl-CoA (39%)
- ○ B. Alanine (7%)
- ○ C. Citrate (12%)
- ○ D. Fructose 2,6-bisphosphate (17%)
- ○ E. Lactate (6%)
- ○ F. Oxaloacetate (16%)

Correct

39% Answered correctly

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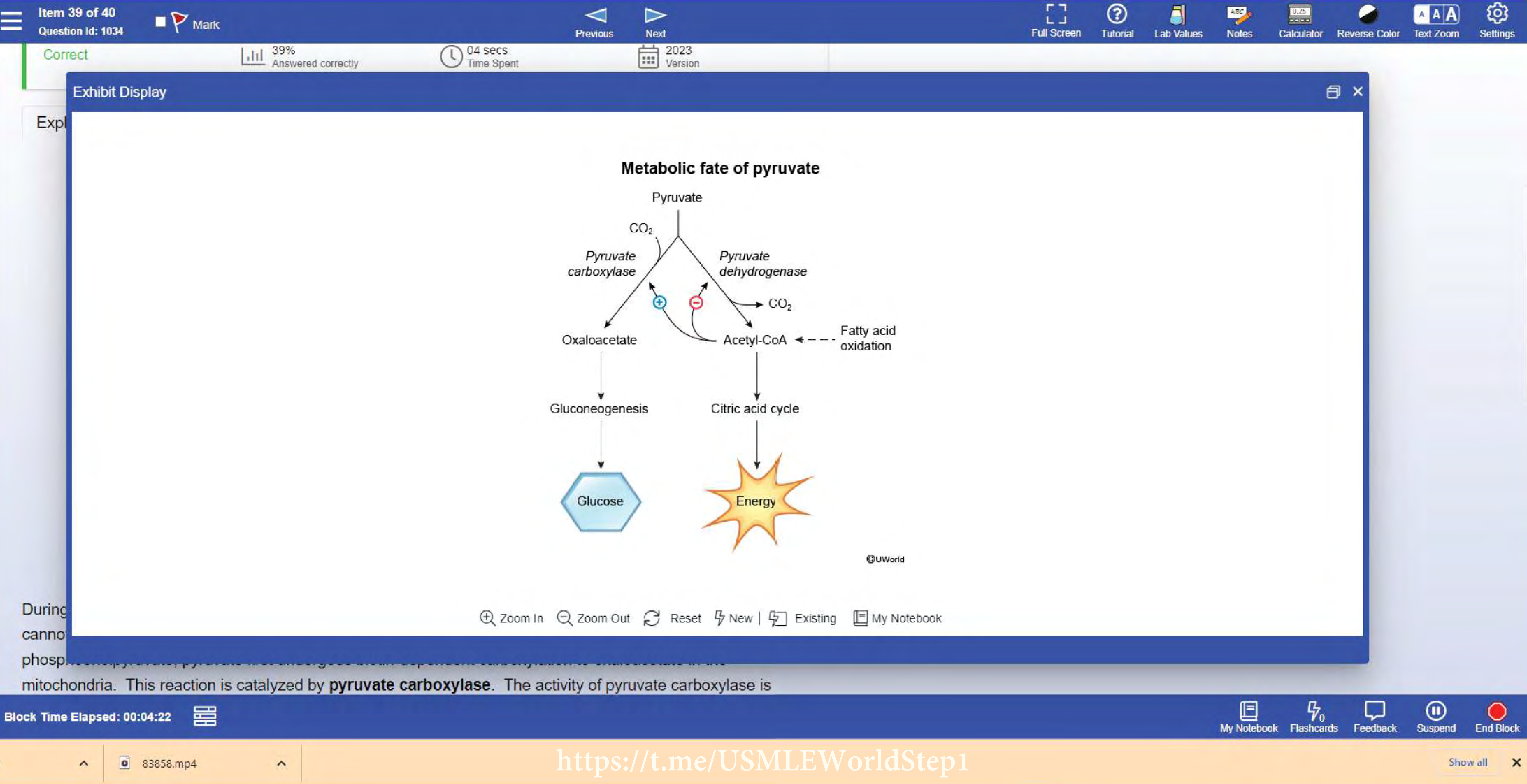
2023 Version

Explanation

Metabolic fate of pyruvate

Pyruvate
CO_2


Item 39 of 40
Question Id: 1034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Pyruvate
CO2
Pyruvate carboxylase
Pyruvate dehydrogenase
CO2
Oxaloacetate
Acetyl-CoA
Fatty acid oxidation
Gluconeogenesis
Citric acid cycle
Glucose
Energy
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Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Correct

39% Answered correctly

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2023 Version

Expl

Metabolic fate of pyruvate

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mitochondria. This reaction is catalyzed by **pyruvate carboxylase**. The activity of pyruvate carboxylase is

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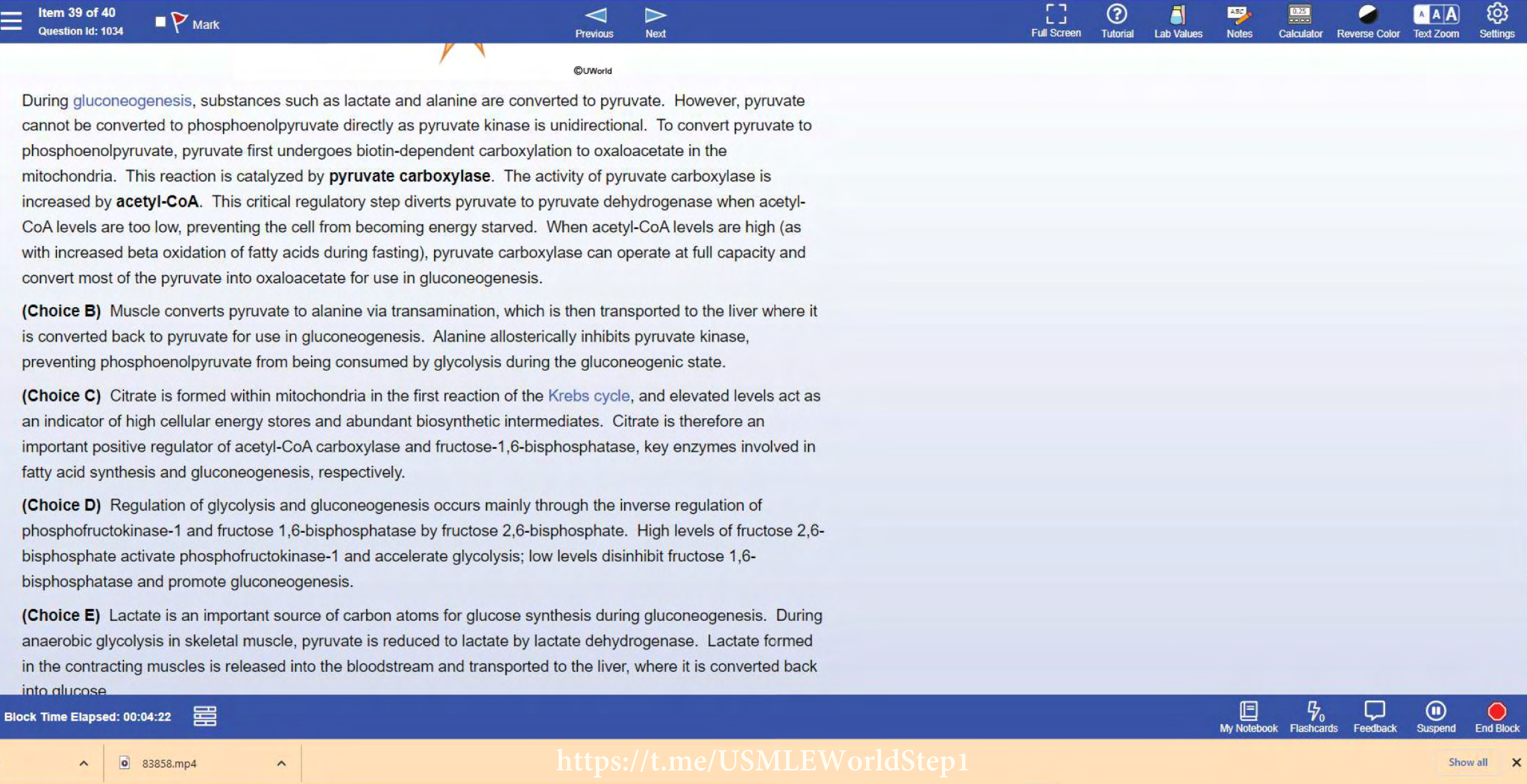


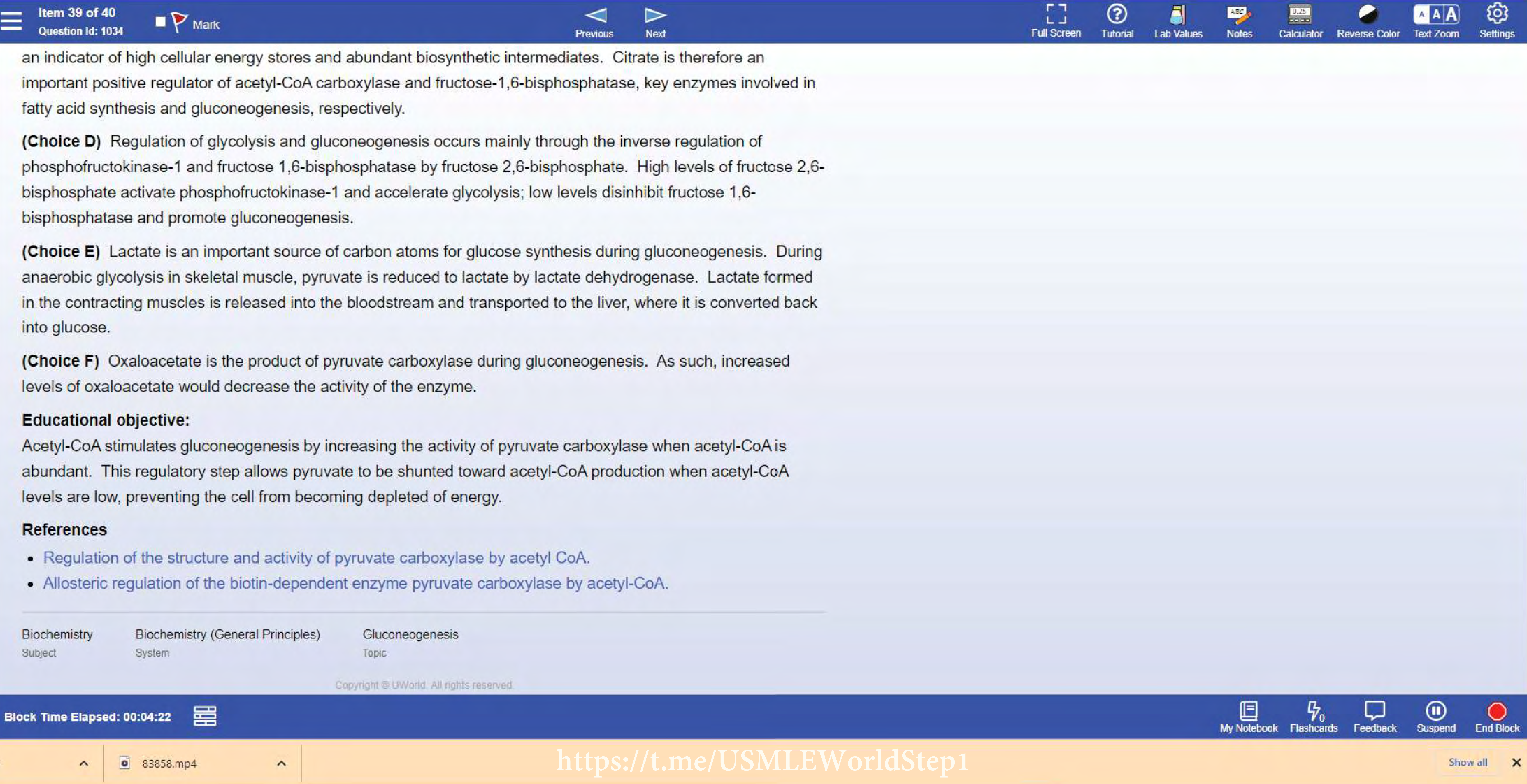
During gluconeogenesis, substances such as lactate and alanine are converted to pyruvate. However, pyruvate cannot be converted to phosphoenolpyruvate directly as pyruvate kinase is unidirectional. To convert pyruvate to phosphoenolpyruvate, pyruvate first undergoes biotin-dependent carboxylation to oxaloacetate in the mitochondria. This reaction is catalyzed by **pyruvate carboxylase**. The activity of pyruvate carboxylase is increased by **acetyl-CoA**. This critical regulatory step diverts pyruvate to pyruvate dehydrogenase when acetyl-CoA levels are too low, preventing the cell from becoming energy starved. When acetyl-CoA levels are high (as with increased beta oxidation of fatty acids during fasting), pyruvate carboxylase can operate at full capacity and convert most of the pyruvate into oxaloacetate for use in gluconeogenesis.

(Choice B) Muscle converts pyruvate to alanine via transamination, which is then transported to the liver where it is converted back to pyruvate for use in gluconeogenesis. Alanine allosterically inhibits pyruvate kinase, preventing phosphoenolpyruvate from being consumed by glycolysis during the gluconeogenic state.

(Choice C) Citrate is formed within mitochondria in the first reaction of the Krebs cycle, and elevated levels act as an indicator of high cellular energy stores and abundant biosynthetic intermediates. Citrate is therefore an important positive regulator of acetyl-CoA carboxylase and fructose-1,6-bisphosphatase, key enzymes involved in fatty acid synthesis and gluconeogenesis, respectively.

(Choice D) Regulation of glycolysis and gluconeogenesis occurs mainly through the inverse regulation of phosphofructokinase-1 and fructose 1,6-bisphosphatase by fructose 2,6-bisphosphate. High levels of fructose 2,6-bisphosphate activate phosphofructokinase-1 and accelerate glycolysis; low levels disinhibit fructose 1,6-bisphosphatase and promote gluconeogenesis.

(Choice E) Lactate is an important source of carbon atoms for glucose synthesis during gluconeogenesis. During anaerobic glycolysis in skeletal muscle, pyruvate is reduced to lactate by lactate dehydrogenase. Lactate formed in the contracting muscles is released into the bloodstream and transported to the liver, where it is converted back into glucose


Item 39 of 40
Question Id: 1034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choice F) Oxaloacetate is the product of pyruvate carboxylase during gluconeogenesis. As such, increased levels of oxaloacetate would decrease the activity of the enzyme.

Educational objective:

Acetyl-CoA stimulates gluconeogenesis by increasing the activity of pyruvate carboxylase when acetyl-CoA is abundant. This regulatory step allows pyruvate to be shunted toward acetyl-CoA production when acetyl-CoA levels are low, preventing the cell from becoming depleted of energy.

References

- Regulation of the structure and activity of pyruvate carboxylase by acetyl CoA.
- Allosteric regulation of the biotin-dependent enzyme pyruvate carboxylase by acetyl-CoA.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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Feedback
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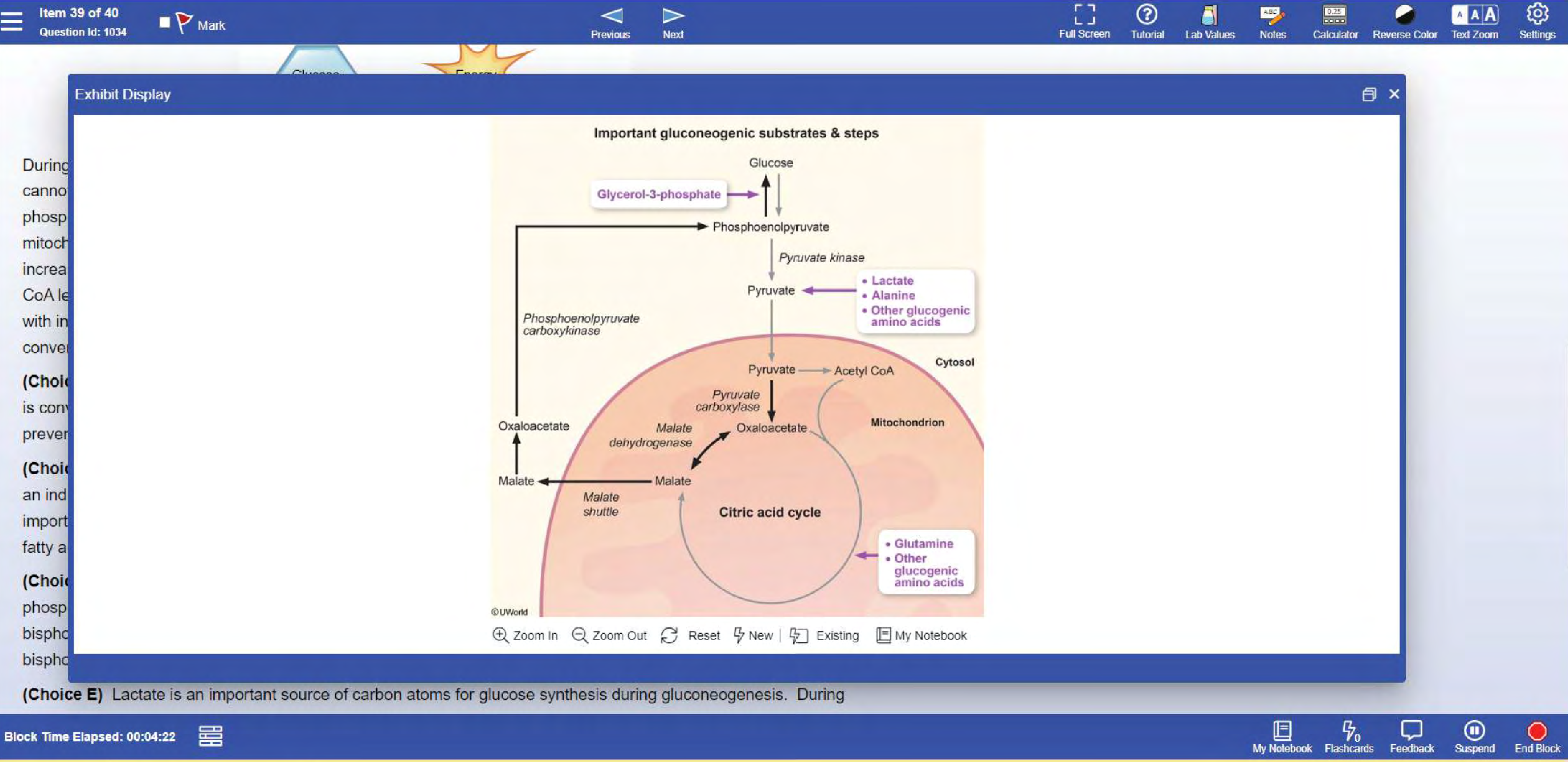
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Glucose
Energy
Exhibit Display
Important gluconeogenic substrates & steps
Glucose
Glycerol-3-phosphate
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
• Lactate
• Alanine
• Other glucogenic amino acids
Phosphoenolpyruvate carboxykinase
Cytosol
Pyruvate
Acetyl CoA
Pyruvate carboxylase
Mitochondrion
Oxaloacetate
Malate dehydrogenase
Oxaloacetate
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Citric acid cycle
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Zoom In
Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block
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Show all

Item 39 of 40
Question Id: 1034

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(Choice E) Lactate is an important source of carbon atoms for glucose synthesis during gluconeogenesis. During

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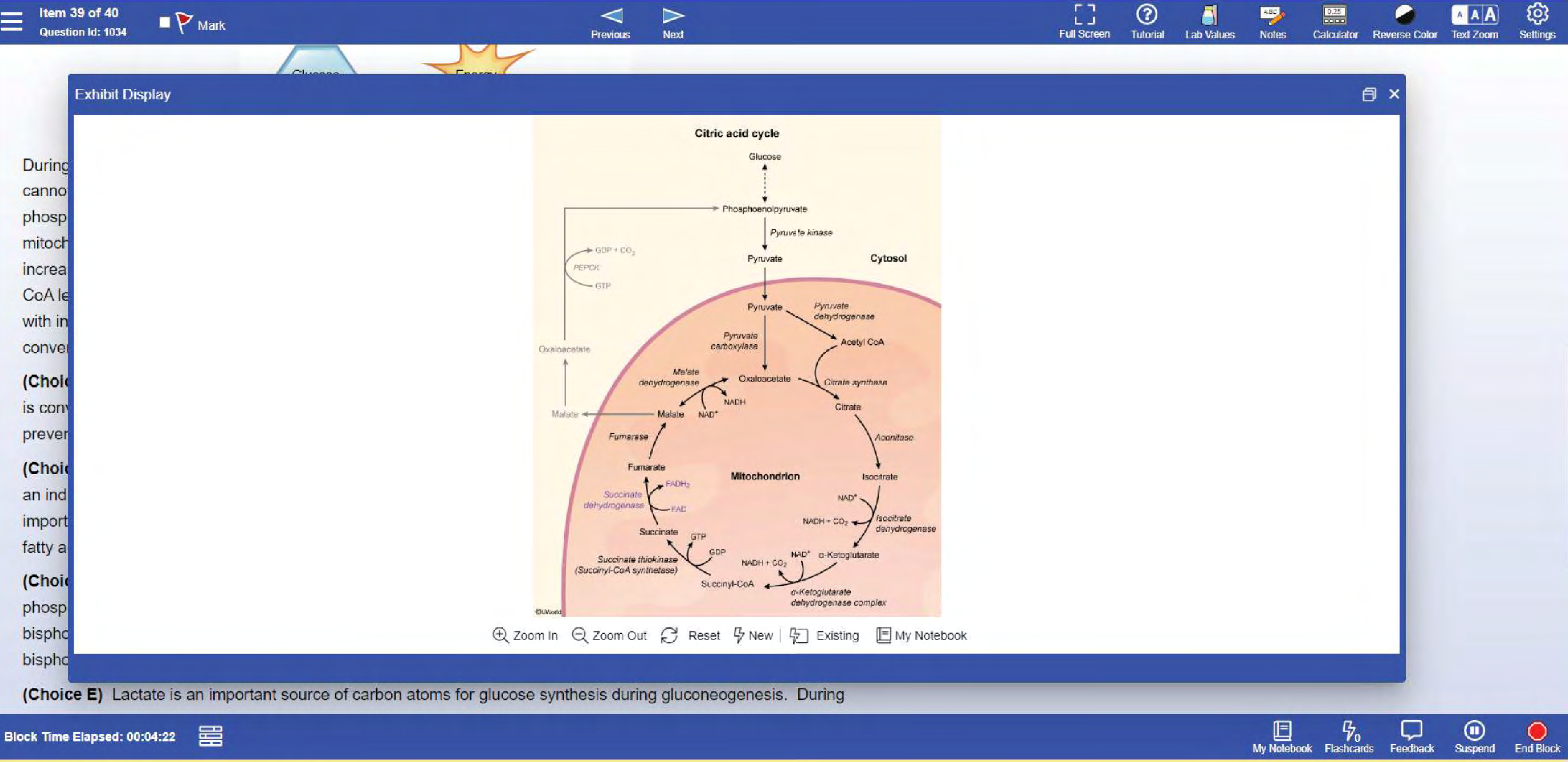
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Mark
Exhibit Display
Citric acid cycle
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Pyruvate kinase
Pyruvate
Cytosol
GDP + CO₂
PEPCK
GTP
Pyruvate
Pyruvate dehydrogenase
Acetyl CoA
Pyruvate carboxylase
Oxaloacetate
Oxaloacetate
Citrate synthase
Malate dehydrogenase
NADH
NAD⁺
Malate
Malate
Citrate
Fumarase
Aconitase
Fumarate
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Succinate dehydrogenase
FAD
NAD⁺
NADH + CO₂
Isocitrate dehydrogenase
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Zoom In
Zoom Out
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Flashcards
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Item 39 of 40
Question Id: 1034

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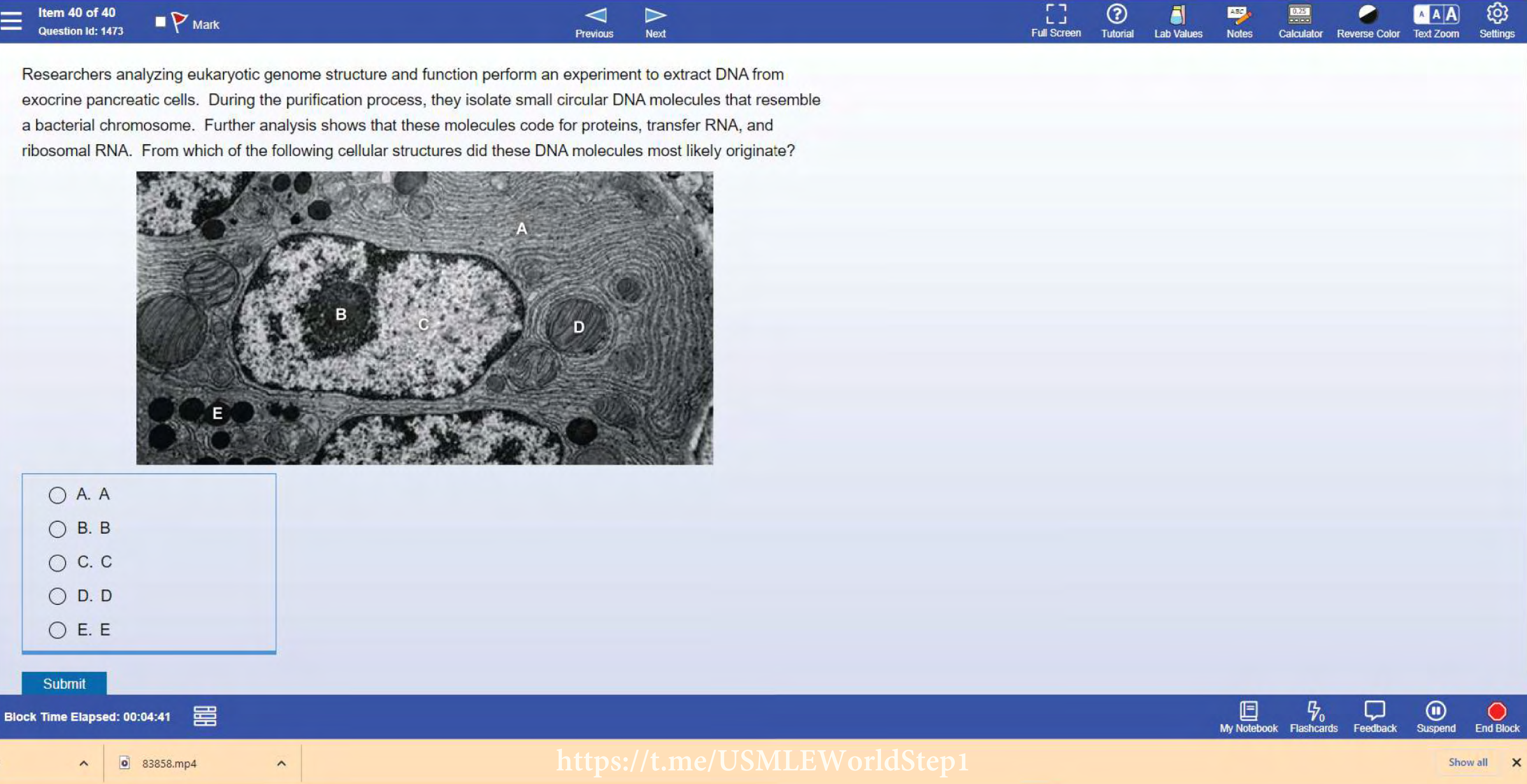
Item 40 of 40
Question Id: 1473
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
End Block
83858.mp4
Show all

Researchers analyzing eukaryotic genome structure and function perform an experiment to extract DNA from exocrine pancreatic cells. During the purification process, they isolate small circular DNA molecules that resemble a bacterial chromosome. Further analysis shows that these molecules code for proteins, transfer RNA, and ribosomal RNA. From which of the following cellular structures did these DNA molecules most likely originate?

○ A. A
○ B. B
○ C. C
○ D. D
○ E. E

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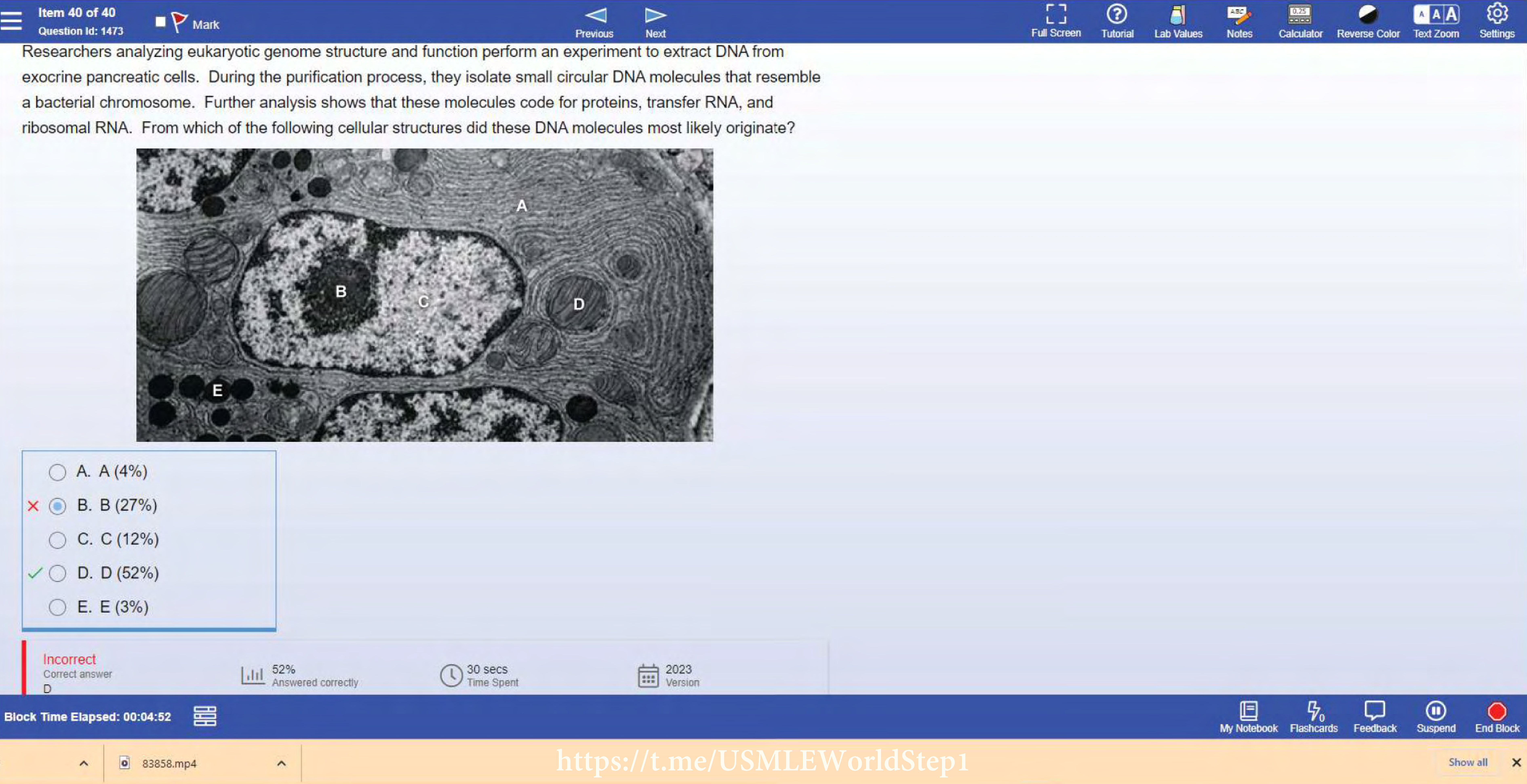
Item 40 of 40
Question Id: 1473
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ A. A (4%)

✗ ● B. B (27%)

○ C. C (12%)

✓ ○ D. D (52%)

○ E. E (3%)

Incorrect
Correct answer
D

52%
Answered correctly

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2023
Version

Item 40 of 40
Question Id: 1473

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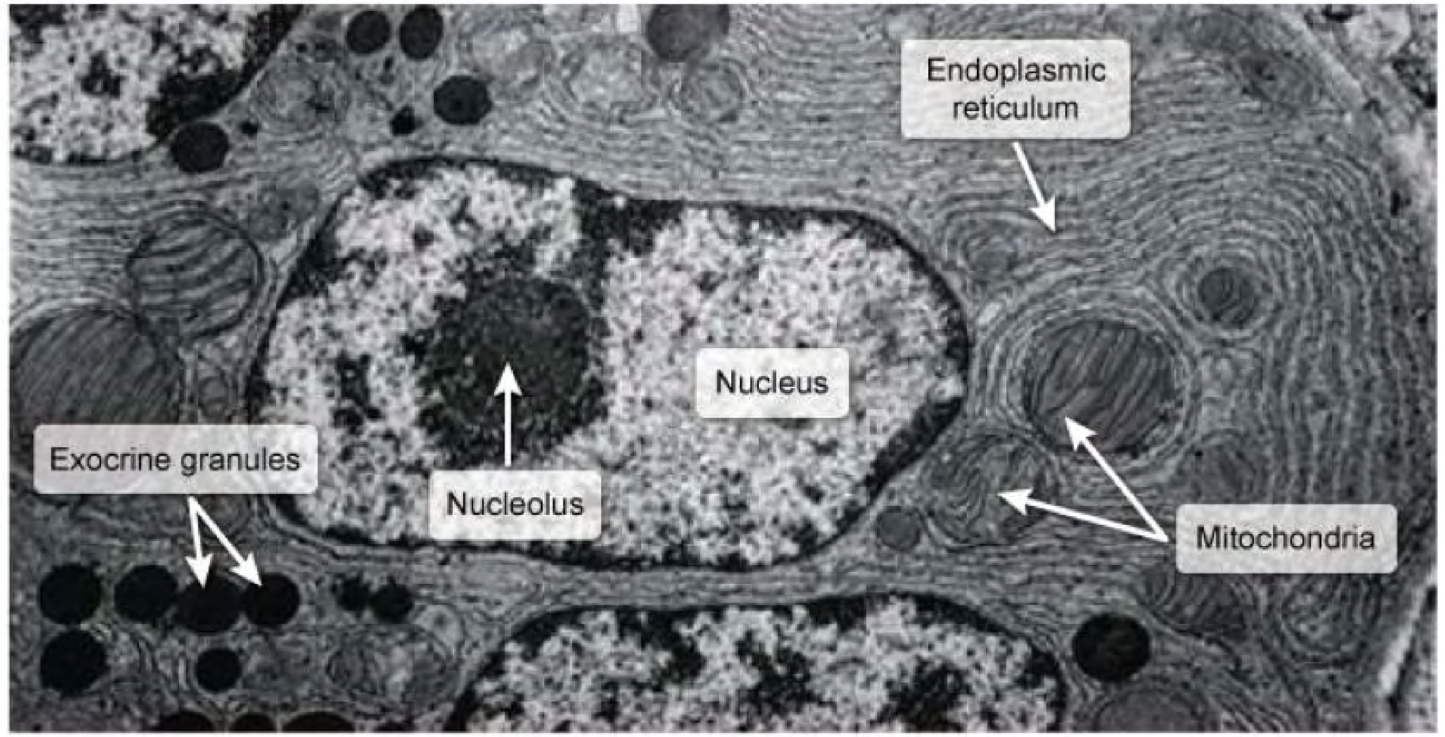
Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Explanation

Exhibit Display

Cellular organelles under electron microscopy


Endoplasmic reticulum
Nucleus
Exocrine granules
Nucleolus
Mitochondria

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mtDNA. As a result, diseases arising from mutations in mtDNA are transmitted from the mother to all of her offspring

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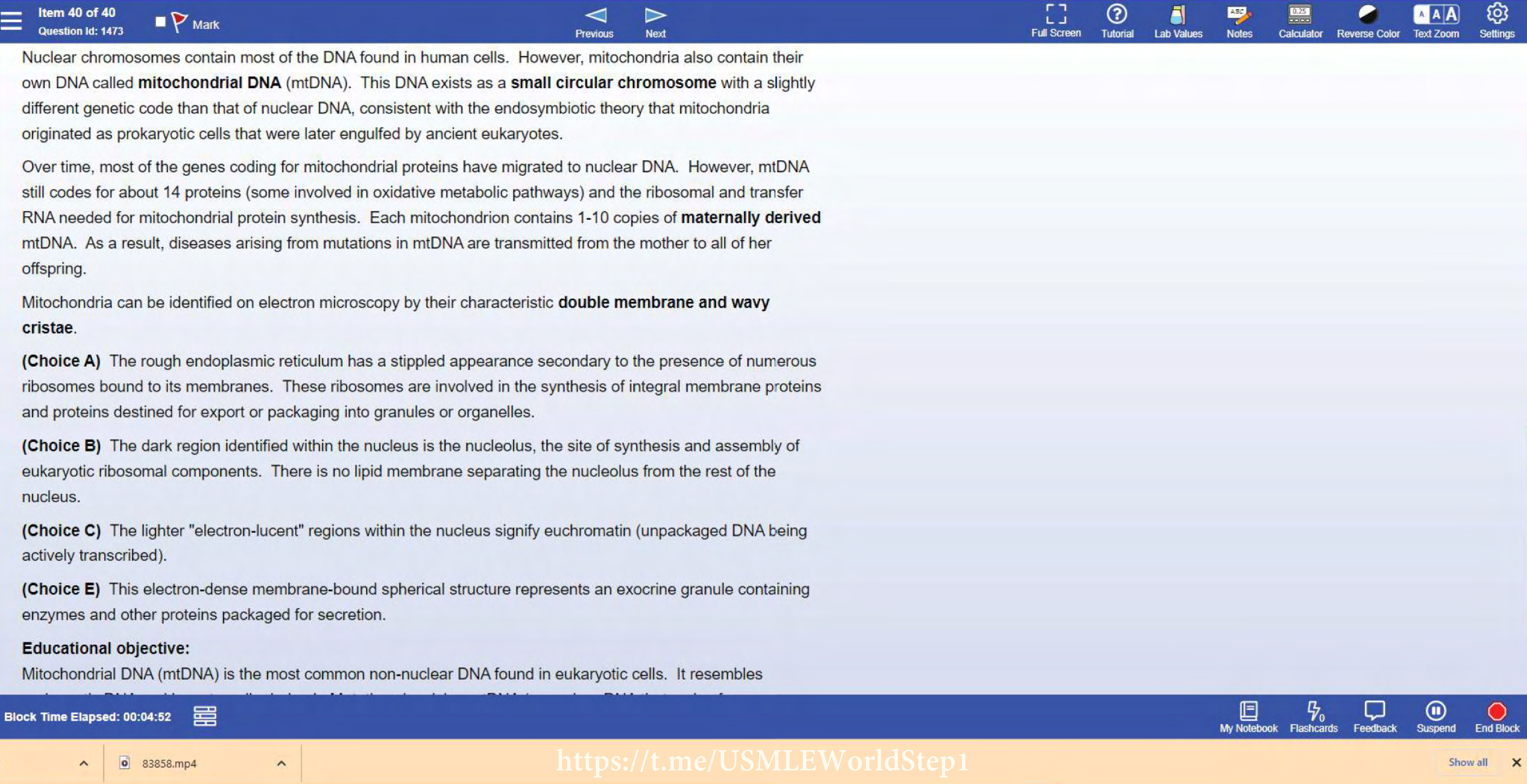
Item 40 of 40
Question Id: 1473
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Nuclear chromosomes contain most of the DNA found in human cells. However, mitochondria also contain their own DNA called **mitochondrial DNA** (mtDNA). This DNA exists as a **small circular chromosome** with a slightly different genetic code than that of nuclear DNA, consistent with the endosymbiotic theory that mitochondria originated as prokaryotic cells that were later engulfed by ancient eukaryotes.

Over time, most of the genes coding for mitochondrial proteins have migrated to nuclear DNA. However, mtDNA still codes for about 14 proteins (some involved in oxidative metabolic pathways) and the ribosomal and transfer RNA needed for mitochondrial protein synthesis. Each mitochondrion contains 1-10 copies of **maternally derived** mtDNA. As a result, diseases arising from mutations in mtDNA are transmitted from the mother to all of her offspring.

Mitochondria can be identified on electron microscopy by their characteristic **double membrane and wavy cristae**.

(Choice A) The rough endoplasmic reticulum has a stippled appearance secondary to the presence of numerous ribosomes bound to its membranes. These ribosomes are involved in the synthesis of integral membrane proteins and proteins destined for export or packaging into granules or organelles.

(Choice B) The dark region identified within the nucleus is the nucleolus, the site of synthesis and assembly of eukaryotic ribosomal components. There is no lipid membrane separating the nucleolus from the rest of the nucleus.

(Choice C) The lighter "electron-lucent" regions within the nucleus signify euchromatin (unpackaged DNA being actively transcribed).

(Choice E) This electron-dense membrane-bound spherical structure represents an exocrine granule containing enzymes and other proteins packaged for secretion.

Educational objective:

Mitochondrial DNA (mtDNA) is the most common non-nuclear DNA found in eukaryotic cells. It resembles

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Feedback
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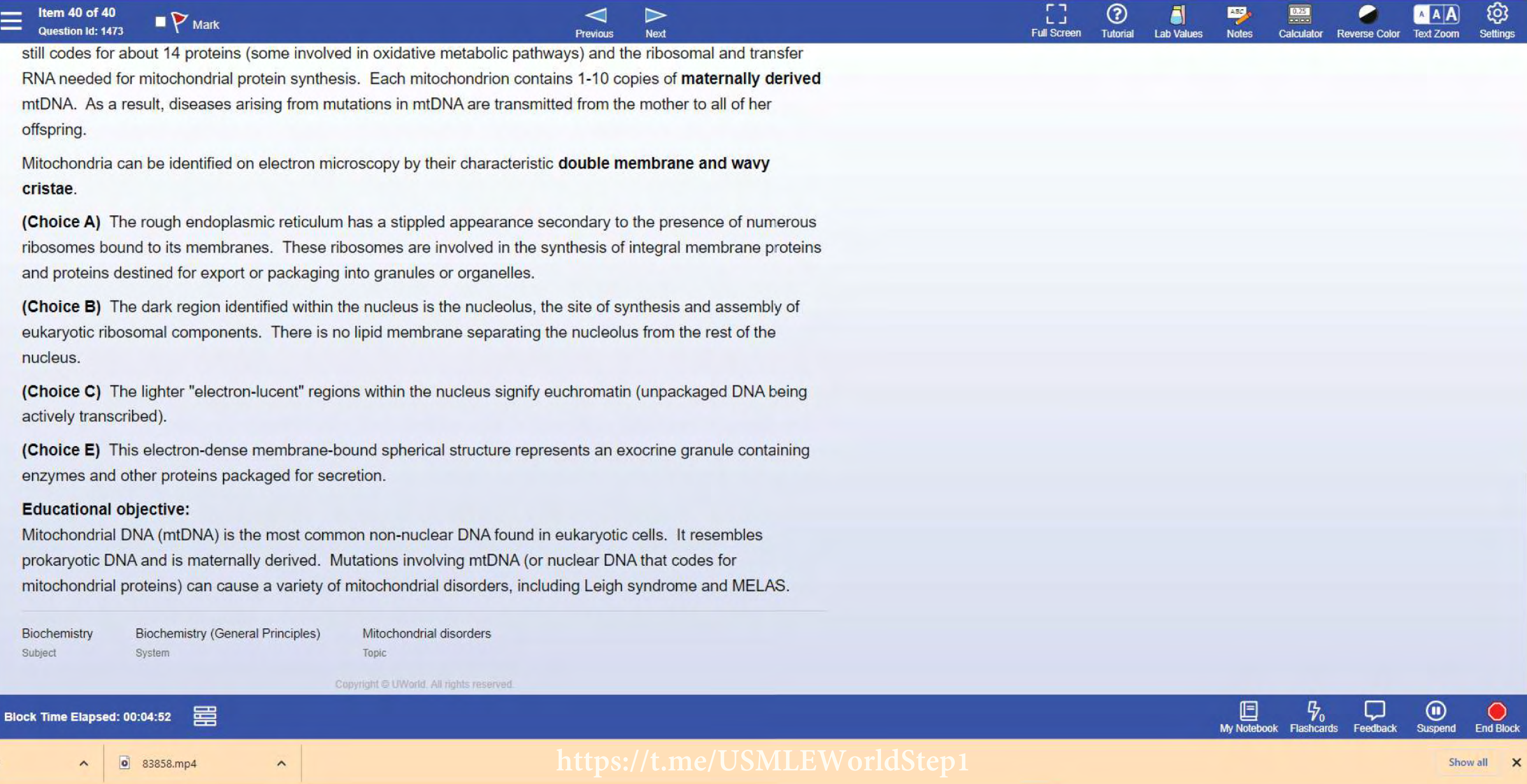
Item 40 of 40
Question Id: 1473
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

still codes for about 14 proteins (some involved in oxidative metabolic pathways) and the ribosomal and transfer RNA needed for mitochondrial protein synthesis. Each mitochondrion contains 1-10 copies of **maternally derived** mtDNA. As a result, diseases arising from mutations in mtDNA are transmitted from the mother to all of her offspring.

Mitochondria can be identified on electron microscopy by their characteristic **double membrane and wavy cristae**.

(Choice A) The rough endoplasmic reticulum has a stippled appearance secondary to the presence of numerous ribosomes bound to its membranes. These ribosomes are involved in the synthesis of integral membrane proteins and proteins destined for export or packaging into granules or organelles.

(Choice B) The dark region identified within the nucleus is the nucleolus, the site of synthesis and assembly of eukaryotic ribosomal components. There is no lipid membrane separating the nucleolus from the rest of the nucleus.

(Choice C) The lighter "electron-lucent" regions within the nucleus signify euchromatin (unpackaged DNA being actively transcribed).

(Choice E) This electron-dense membrane-bound spherical structure represents an exocrine granule containing enzymes and other proteins packaged for secretion.

Educational objective:

Mitochondrial DNA (mtDNA) is the most common non-nuclear DNA found in eukaryotic cells. It resembles prokaryotic DNA and is maternally derived. Mutations involving mtDNA (or nuclear DNA that codes for mitochondrial proteins) can cause a variety of mitochondrial disorders, including Leigh syndrome and MELAS.

Biochemistry	Biochemistry (General Principles)	Mitochondrial disorders
Subject	System	Topic

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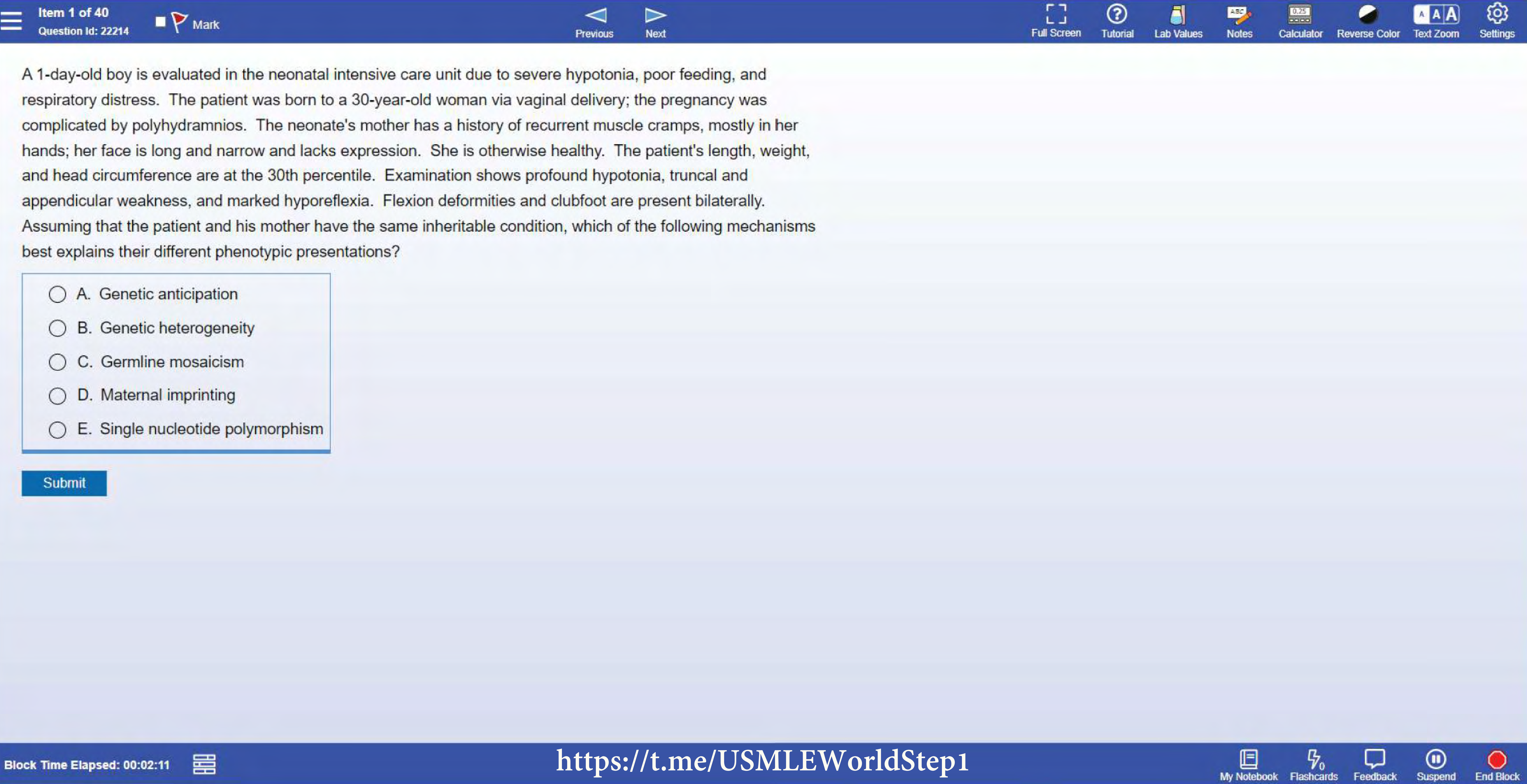
Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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A 1-day-old boy is evaluated in the neonatal intensive care unit due to severe hypotonia, poor feeding, and respiratory distress. The patient was born to a 30-year-old woman via vaginal delivery; the pregnancy was complicated by polyhydramnios. The neonate's mother has a history of recurrent muscle cramps, mostly in her hands; her face is long and narrow and lacks expression. She is otherwise healthy. The patient's length, weight, and head circumference are at the 30th percentile. Examination shows profound hypotonia, truncal and appendicular weakness, and marked hyporeflexia. Flexion deformities and clubfoot are present bilaterally. Assuming that the patient and his mother have the same inheritable condition, which of the following mechanisms best explains their different phenotypic presentations?

○ A. Genetic anticipation
○ B. Genetic heterogeneity
○ C. Germline mosaicism
○ D. Maternal imprinting
○ E. Single nucleotide polymorphism

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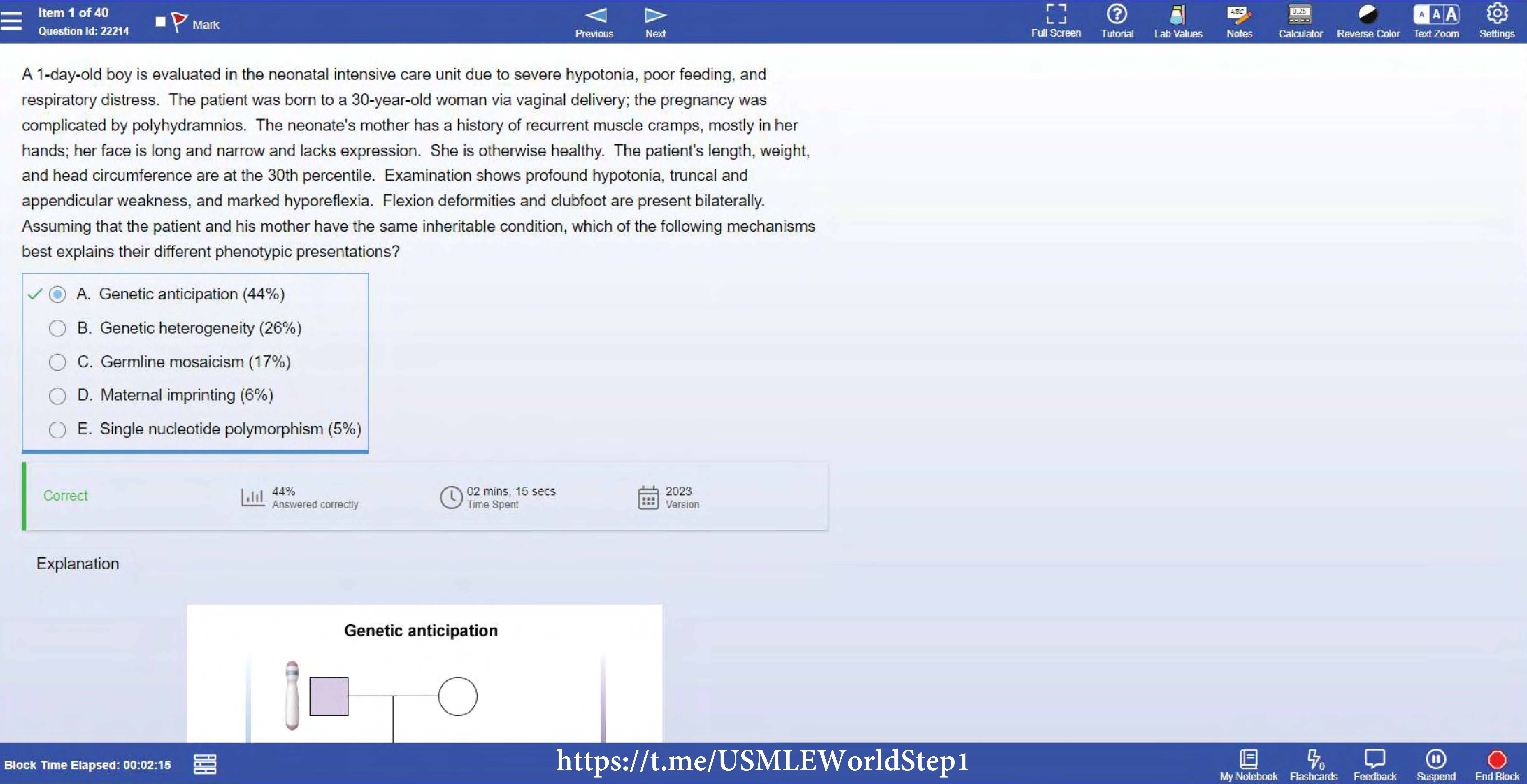
Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
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Text Zoom
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- ✓ ● A. Genetic anticipation (44%)
- ○ B. Genetic heterogeneity (26%)
- ○ C. Germline mosaicism (17%)
- ○ D. Maternal imprinting (6%)
- ○ E. Single nucleotide polymorphism (5%)

Correct

44% Answered correctly

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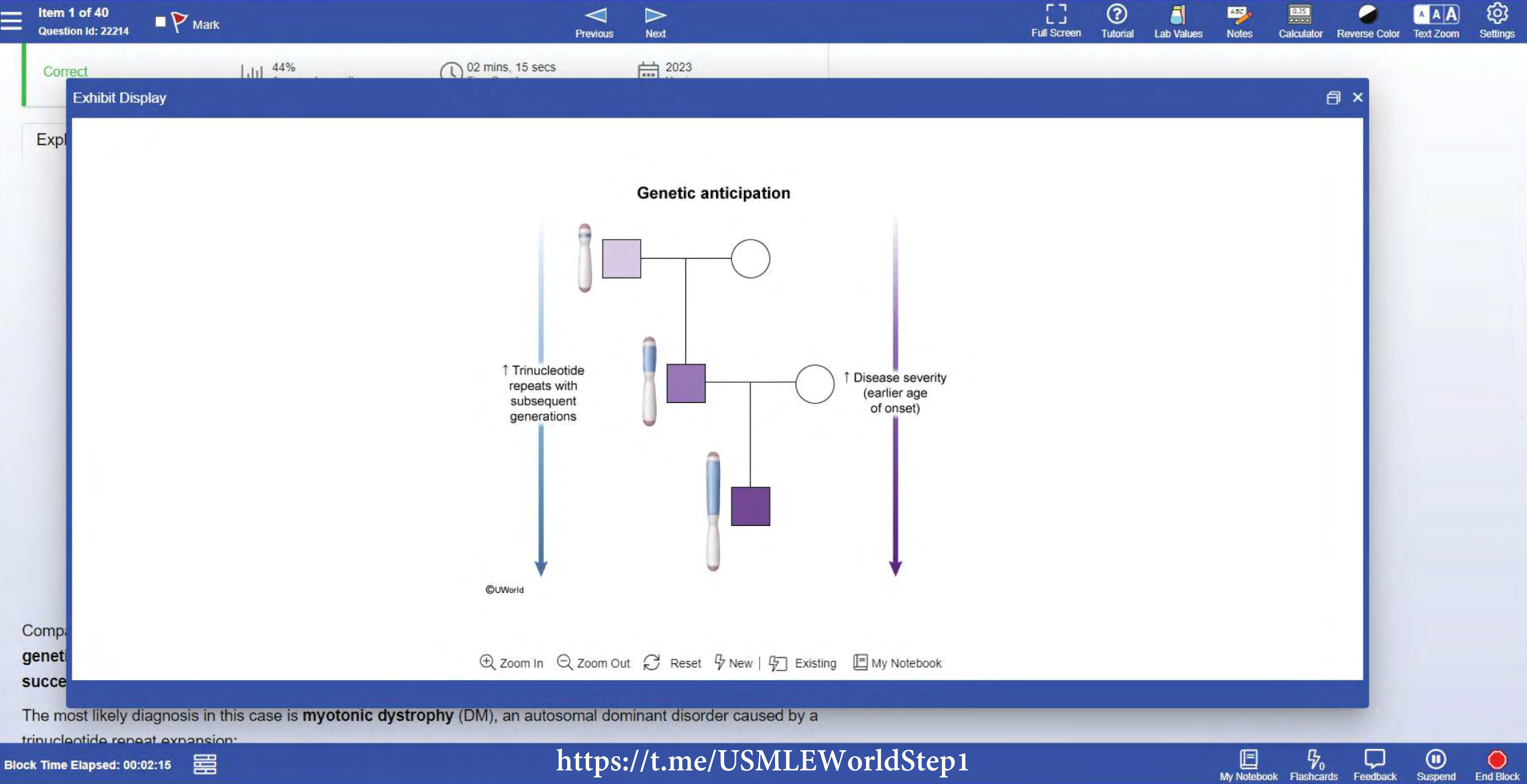
2023 Version

Explanation

Genetic anticipation


Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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Correct
44%
02 mins, 15 secs
2023
Exhibit Display
Genetic anticipation
↑ Trinucleotide repeats with subsequent generations
↑ Disease severity (earlier age of onset)
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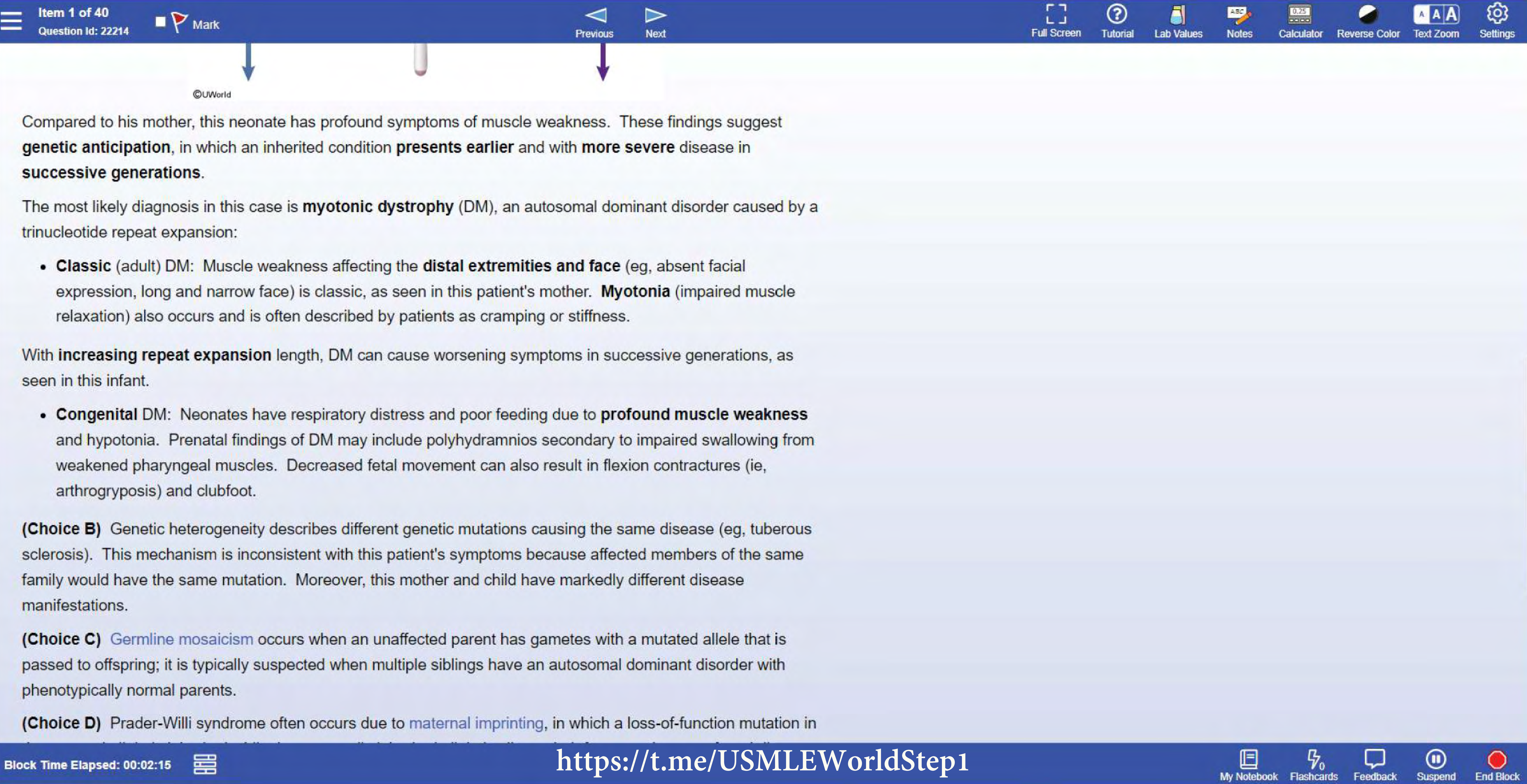
The most likely diagnosis in this case is **myotonic dystrophy** (DM), an autosomal dominant disorder caused by a trinucleotide repeat expansion:


Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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Text Zoom
Settings
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Block Time Elapsed: 00:02:15
My Notebook
Flashcards
Feedback
Suspend
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Compared to his mother, this neonate has profound symptoms of muscle weakness. These findings suggest **genetic anticipation**, in which an inherited condition **presents earlier** and with **more severe** disease in **successive generations**.

The most likely diagnosis in this case is **myotonic dystrophy** (DM), an autosomal dominant disorder caused by a trinucleotide repeat expansion:

- **Classic** (adult) DM: Muscle weakness affecting the **distal extremities and face** (eg, absent facial expression, long and narrow face) is classic, as seen in this patient's mother. **Myotonia** (impaired muscle relaxation) also occurs and is often described by patients as cramping or stiffness.

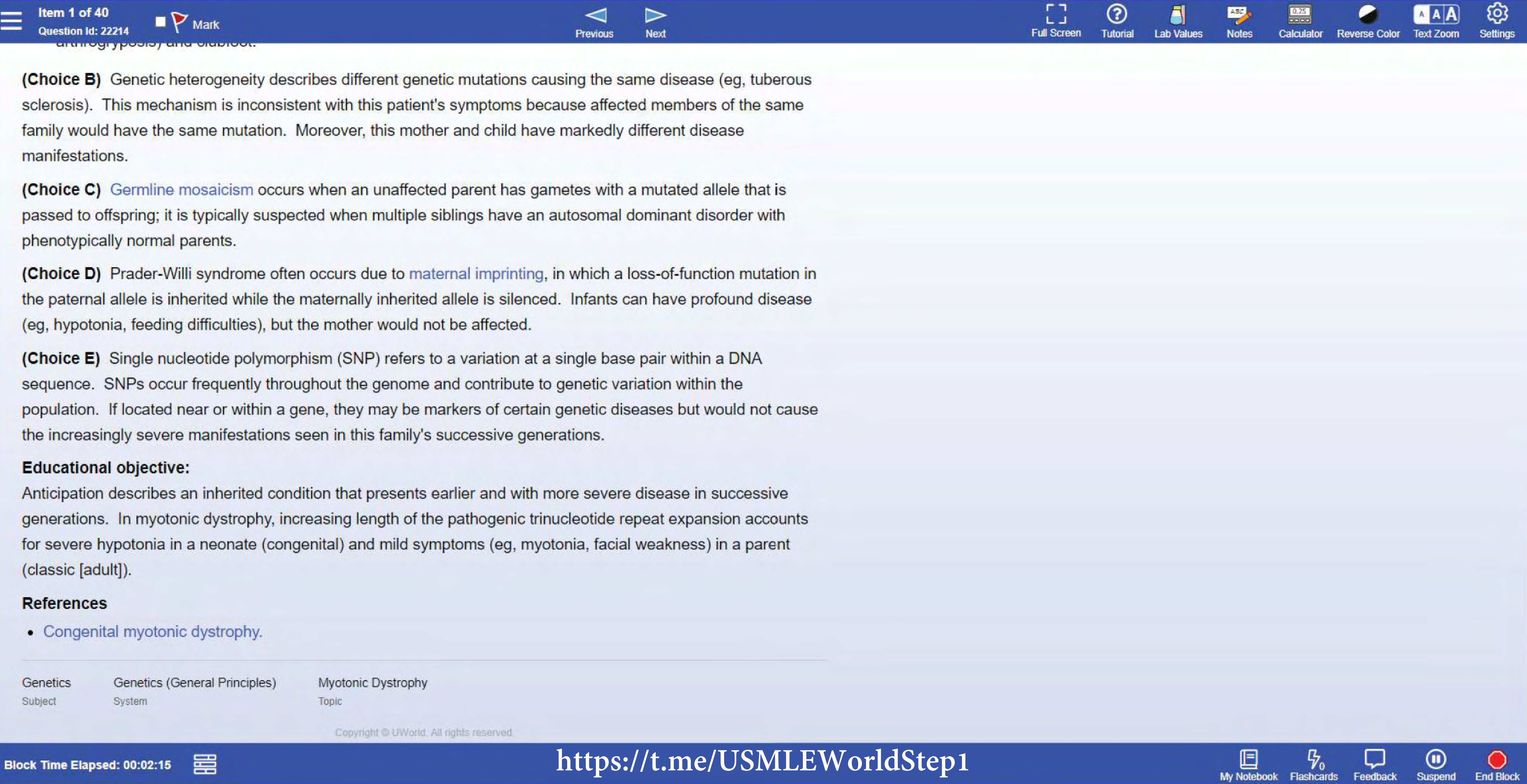
With **increasing repeat expansion** length, DM can cause worsening symptoms in successive generations, as seen in this infant.

- **Congenital** DM: Neonates have respiratory distress and poor feeding due to **profound muscle weakness** and hypotonia. Prenatal findings of DM may include polyhydramnios secondary to impaired swallowing from weakened pharyngeal muscles. Decreased fetal movement can also result in flexion contractures (ie, arthrogryposis) and clubfoot.

(Choice B) Genetic heterogeneity describes different genetic mutations causing the same disease (eg, tuberous sclerosis). This mechanism is inconsistent with this patient's symptoms because affected members of the same family would have the same mutation. Moreover, this mother and child have markedly different disease manifestations.

(Choice C) Germline mosaicism occurs when an unaffected parent has gametes with a mutated allele that is passed to offspring; it is typically suspected when multiple siblings have an autosomal dominant disorder with phenotypically normal parents.

(Choice D) Prader-Willi syndrome often occurs due to maternal imprinting, in which a loss-of-function mutation in


Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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Settings
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Flashcards
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arthrogryposis) and clubfoot.

(Choice B) Genetic heterogeneity describes different genetic mutations causing the same disease (eg, tuberous sclerosis). This mechanism is inconsistent with this patient's symptoms because affected members of the same family would have the same mutation. Moreover, this mother and child have markedly different disease manifestations.

(Choice C) Germline mosaicism occurs when an unaffected parent has gametes with a mutated allele that is passed to offspring; it is typically suspected when multiple siblings have an autosomal dominant disorder with phenotypically normal parents.

(Choice D) Prader-Willi syndrome often occurs due to maternal imprinting, in which a loss-of-function mutation in the paternal allele is inherited while the maternally inherited allele is silenced. Infants can have profound disease (eg, hypotonia, feeding difficulties), but the mother would not be affected.

(Choice E) Single nucleotide polymorphism (SNP) refers to a variation at a single base pair within a DNA sequence. SNPs occur frequently throughout the genome and contribute to genetic variation within the population. If located near or within a gene, they may be markers of certain genetic diseases but would not cause the increasingly severe manifestations seen in this family's successive generations.

Educational objective:

Anticipation describes an inherited condition that presents earlier and with more severe disease in successive generations. In myotonic dystrophy, increasing length of the pathogenic trinucleotide repeat expansion accounts for severe hypotonia in a neonate (congenital) and mild symptoms (eg, myotonia, facial weakness) in a parent (classic [adult]).

References

- Congenital myotonic dystrophy.

Genetics	Genetics (General Principles)	Myotonic Dystrophy
Subject	System	Topic

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arthrogryposis) and clubfoot.

(Choice B) Genetic heterogeneity describes different genetic mutations causing the same disease (eg, tuberous

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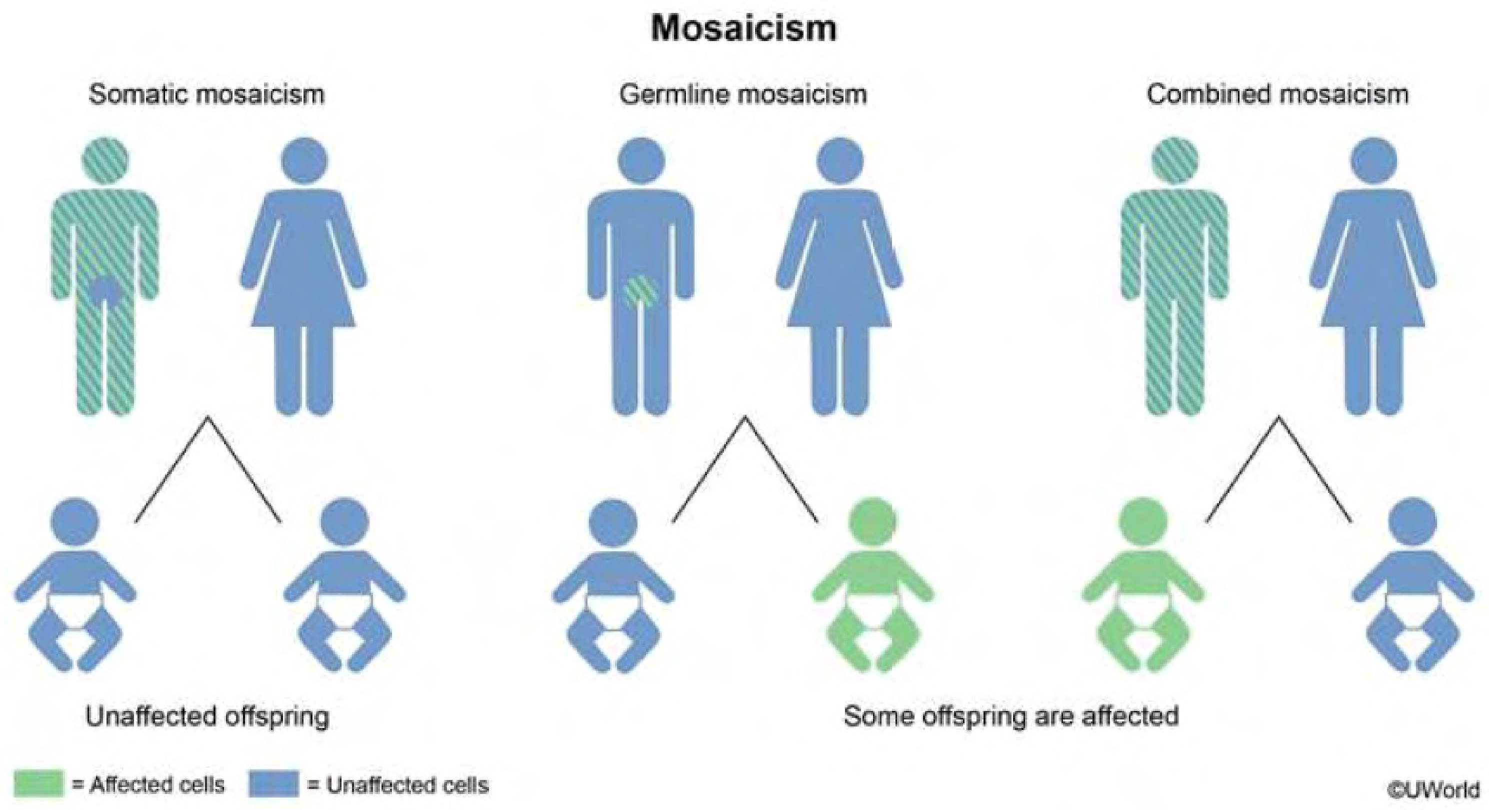
Mosaicism
Somatic mosaicism
Germline mosaicism
Combined mosaicism
Unaffected offspring
Some offspring are affected
🟩 = Affected cells
🟦 = Unaffected cells
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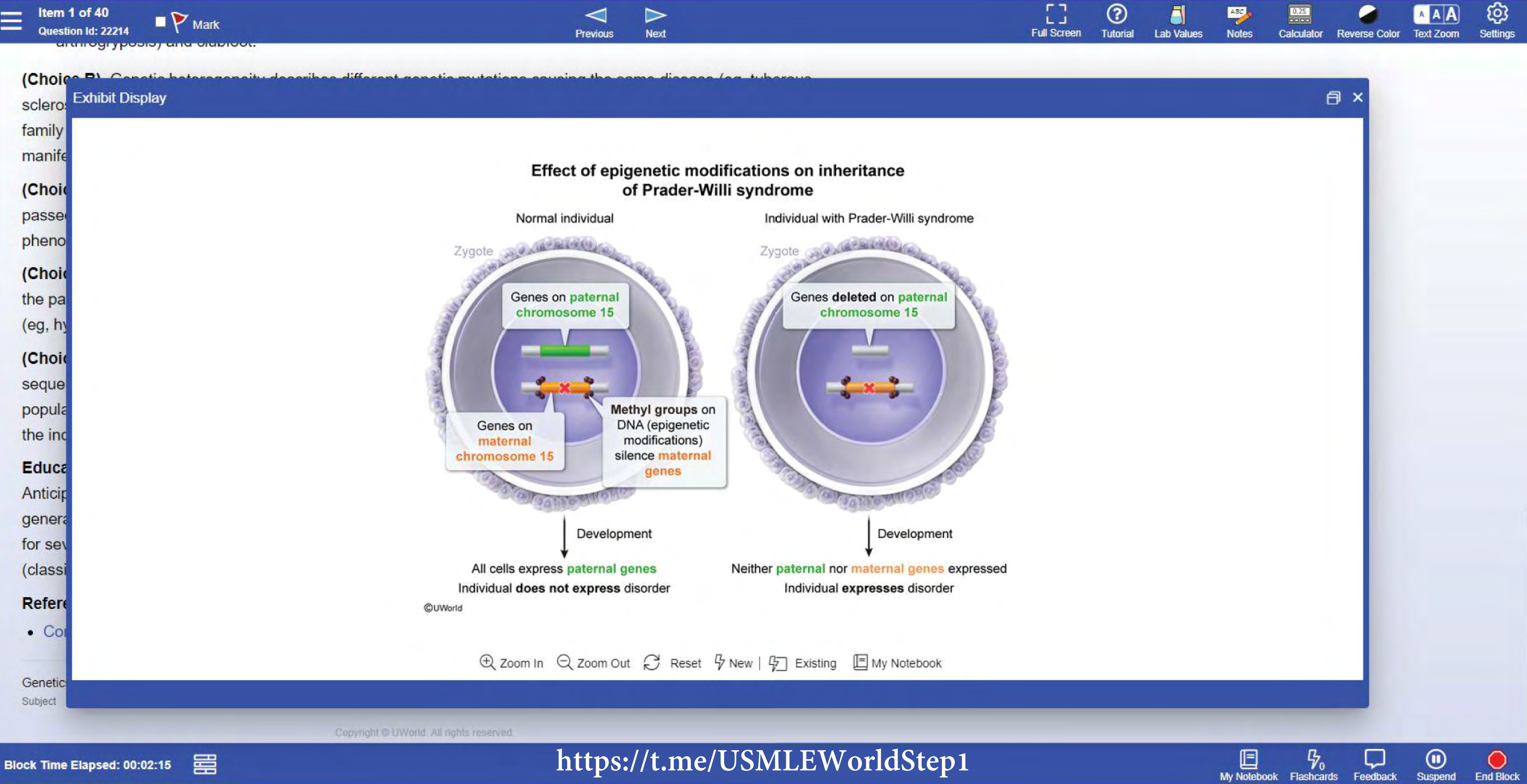

Item 1 of 40
Question Id: 22214
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Genetic

Subject

Exhibit Display

Effect of epigenetic modifications on inheritance of Prader-Willi syndrome

Normal individual
Zygote
Genes on paternal chromosome 15
Genes on maternal chromosome 15
Methyl groups on DNA (epigenetic modifications) silence maternal genes
Development
Individual with Prader-Willi syndrome
Zygote
Genes deleted on paternal chromosome 15
Development

All cells express paternal genes
Individual **does not express** disorder

Neither paternal nor maternal genes expressed
Individual **expresses** disorder

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Reset
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Existing
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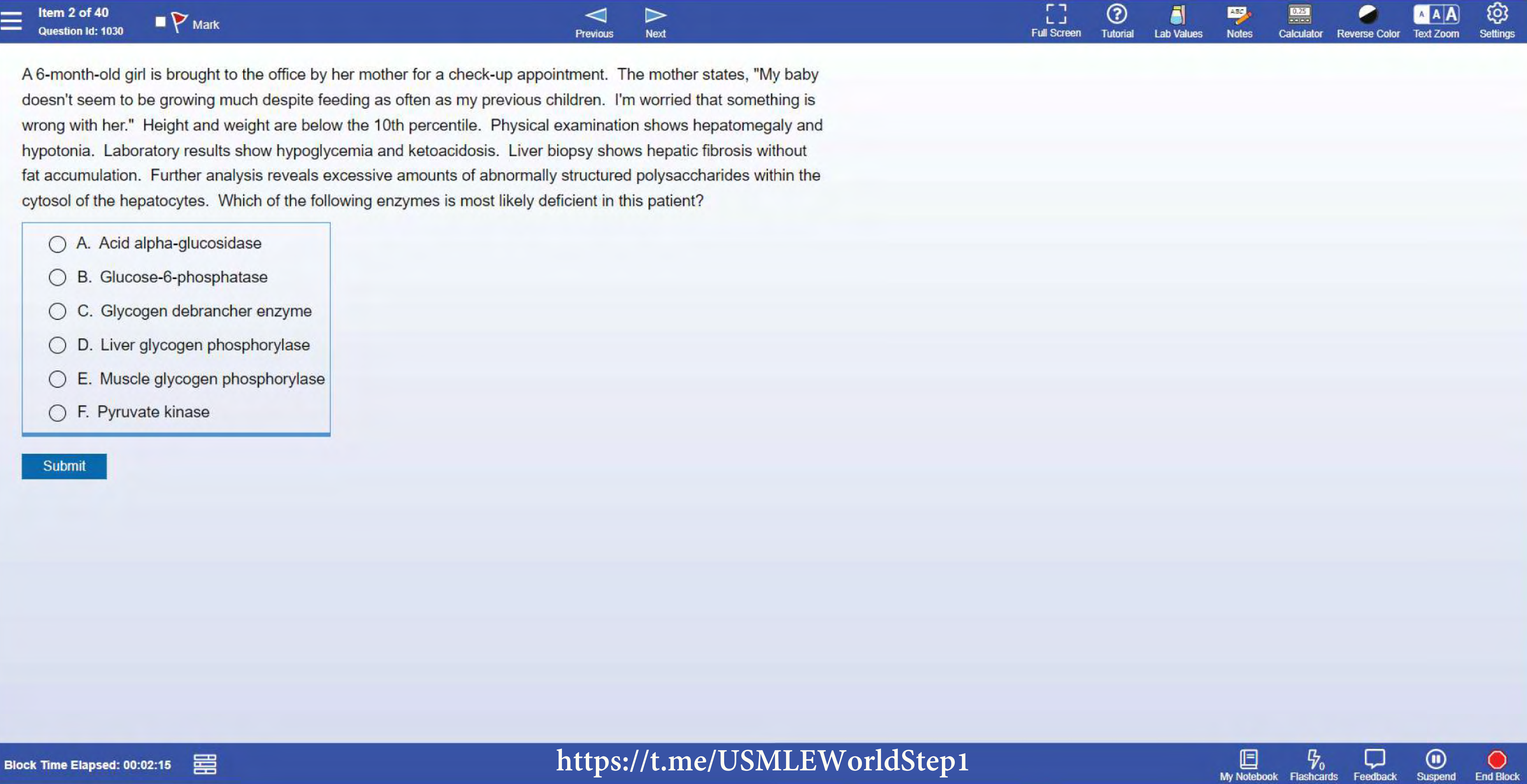
Item 2 of 40
Question Id: 1030
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
End Block

A 6-month-old girl is brought to the office by her mother for a check-up appointment. The mother states, "My baby doesn't seem to be growing much despite feeding as often as my previous children. I'm worried that something is wrong with her." Height and weight are below the 10th percentile. Physical examination shows hepatomegaly and hypotonia. Laboratory results show hypoglycemia and ketoacidosis. Liver biopsy shows hepatic fibrosis without fat accumulation. Further analysis reveals excessive amounts of abnormally structured polysaccharides within the cytosol of the hepatocytes. Which of the following enzymes is most likely deficient in this patient?

○ A. Acid alpha-glucosidase
○ B. Glucose-6-phosphatase
○ C. Glycogen debrancher enzyme
○ D. Liver glycogen phosphorylase
○ E. Muscle glycogen phosphorylase
○ F. Pyruvate kinase

Submit

A 6-month-old girl is brought to the office by her mother for a check-up appointment. The mother states, "My baby doesn't seem to be growing much despite feeding as often as my previous children. I'm worried that something is wrong with her." Height and weight are below the 10th percentile. Physical examination shows hepatomegaly and hypotonia. Laboratory results show hypoglycemia and ketoacidosis. Liver biopsy shows hepatic fibrosis without fat accumulation. Further analysis reveals excessive amounts of abnormally structured polysaccharides within the cytosol of the hepatocytes. Which of the following enzymes is most likely deficient in this patient?

○ A. Acid alpha-glucosidase (6%)
✗ ● B. Glucose-6-phosphatase (24%)
✓ ○ C. Glycogen debrancher enzyme (45%)
○ D. Liver glycogen phosphorylase (19%)
○ E. Muscle glycogen phosphorylase (1%)
○ F. Pyruvate kinase (1%)

Incorrect
Correct answer
C

45%
Answered correctly

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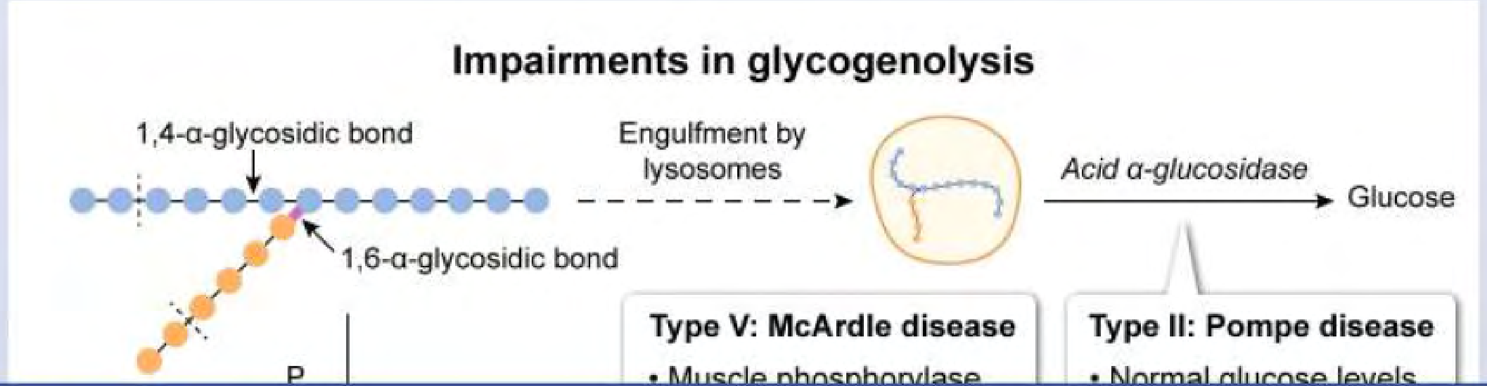
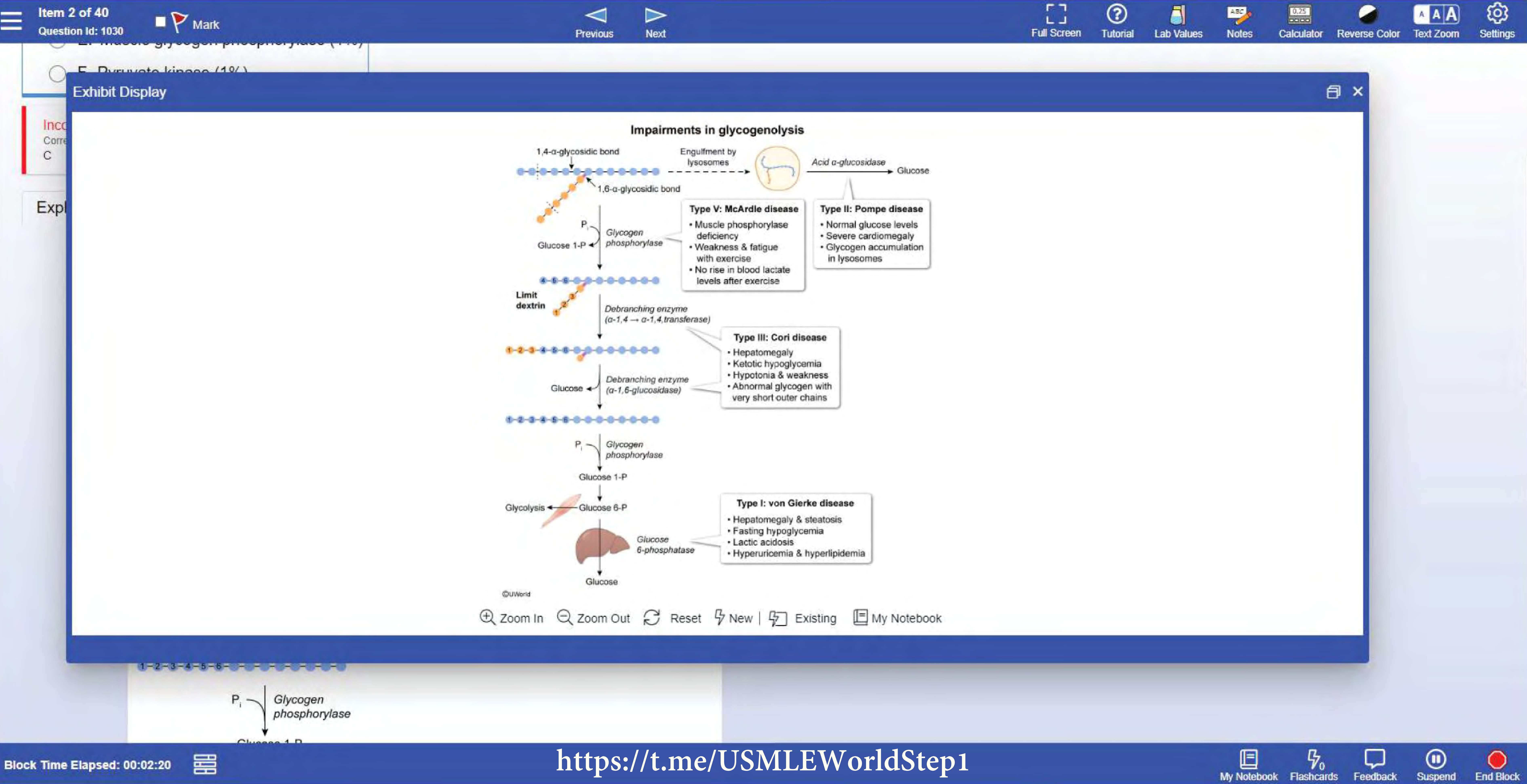
Explanation


Impairments in glycogenolysis
1,4-α-glycosidic bond
1,6-α-glycosidic bond
Engulfment by lysosomes
Acid α-glucosidase
Glucose
P
Type V: McArdle disease
• Muscle phosphorylase
Type II: Pompe disease
• Normal glucose levels


Item 2 of 40
Question Id: 1030
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ E. Pyruvate kinase (1%)
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1,4-α-glycosidic bond
Engulfment by lysosomes
Acid α-glucosidase
Glucose
1,6-α-glycosidic bond
P_i
Glycogen phosphorylase
Glucose 1-P
Limit dextrin
Debranching enzyme (α-1,4 → α-1,4,transferase)
Glucose
Debranching enzyme (α-1,6-glucosidase)
P_i
Glycogen phosphorylase
Glucose 1-P
Glycolysis
Glucose 6-P
Glucose 6-phosphatase
Glucose
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Zoom Out
Reset
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Existing
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Glycogen phosphorylase
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Flashcards
Feedback
Suspend
End Block

Impairments in glycogenolysis

Type V: McArdle disease
- Muscle phosphorylase deficiency
- Weakness & fatigue with exercise
- No rise in blood lactate levels after exercise

Type II: Pompe disease
- Normal glucose levels
- Severe cardiomegaly
- Glycogen accumulation in lysosomes

Type III: Cori disease
- Hepatomegaly
- Ketotic hypoglycemia
- Hypotonia & weakness
- Abnormal glycogen with very short outer chains

Type I: von Gierke disease
- Hepatomegaly & steatosis
- Fasting hypoglycemia
- Lactic acidosis
- Hyperuricemia & hyperlipidemia

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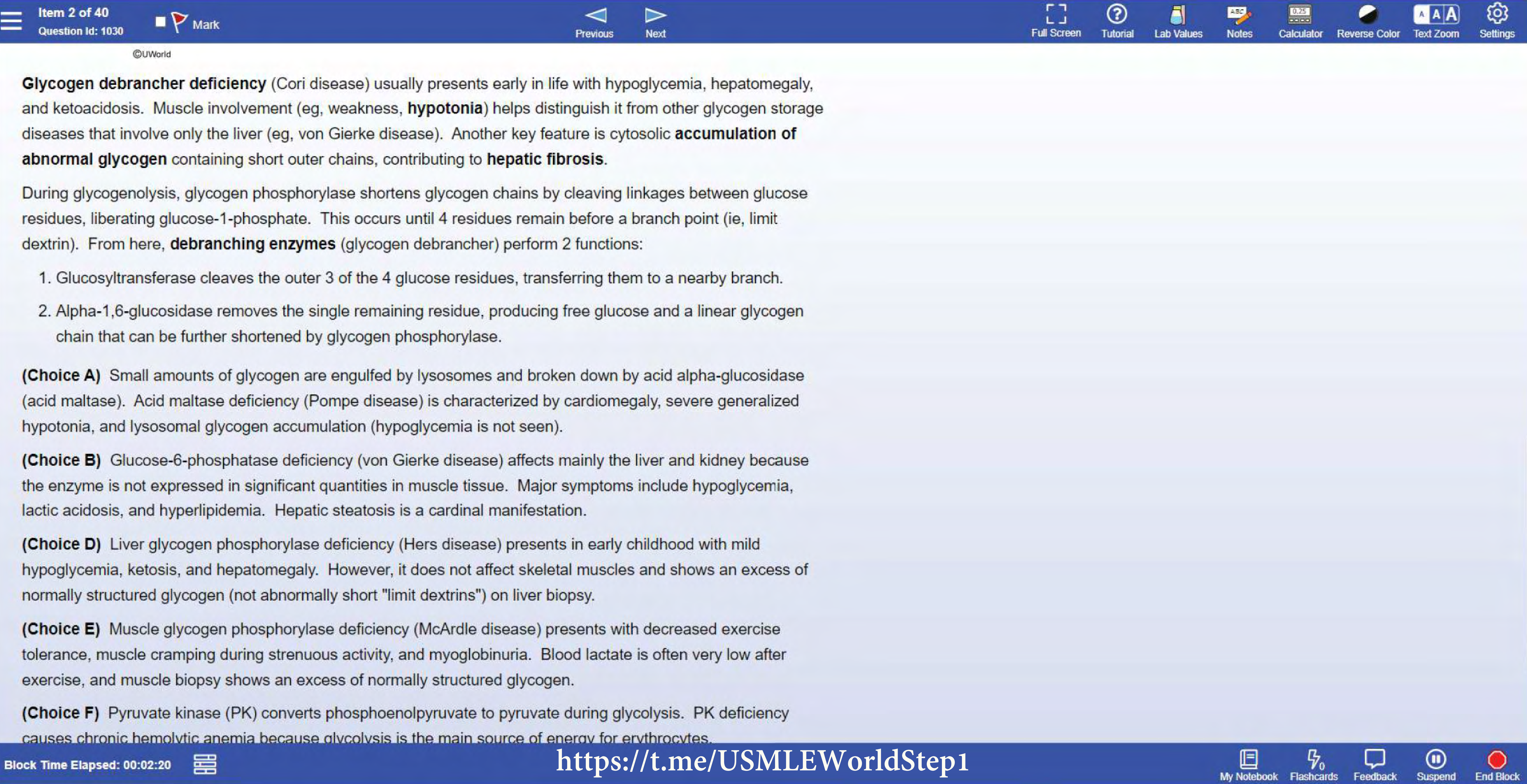

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Glycogen debrancher deficiency (Cori disease) usually presents early in life with hypoglycemia, hepatomegaly, and ketoacidosis. Muscle involvement (eg, weakness, **hypotonia**) helps distinguish it from other glycogen storage diseases that involve only the liver (eg, von Gierke disease). Another key feature is cytosolic **accumulation of abnormal glycogen** containing short outer chains, contributing to **hepatic fibrosis**.

During glycogenolysis, glycogen phosphorylase shortens glycogen chains by cleaving linkages between glucose residues, liberating glucose-1-phosphate. This occurs until 4 residues remain before a branch point (ie, limit dextrin). From here, **debranching enzymes** (glycogen debrancher) perform 2 functions:

1. Glucosyltransferase cleaves the outer 3 of the 4 glucose residues, transferring them to a nearby branch.
2. Alpha-1,6-glucosidase removes the single remaining residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase.

(Choice A) Small amounts of glycogen are engulfed by lysosomes and broken down by acid alpha-glucosidase (acid maltase). Acid maltase deficiency (Pompe disease) is characterized by cardiomegaly, severe generalized hypotonia, and lysosomal glycogen accumulation (hypoglycemia is not seen).

(Choice B) Glucose-6-phosphatase deficiency (von Gierke disease) affects mainly the liver and kidney because the enzyme is not expressed in significant quantities in muscle tissue. Major symptoms include hypoglycemia, lactic acidosis, and hyperlipidemia. Hepatic steatosis is a cardinal manifestation.

(Choice D) Liver glycogen phosphorylase deficiency (Hers disease) presents in early childhood with mild hypoglycemia, ketosis, and hepatomegaly. However, it does not affect skeletal muscles and shows an excess of normally structured glycogen (not abnormally short "limit dextrins") on liver biopsy.

(Choice E) Muscle glycogen phosphorylase deficiency (McArdle disease) presents with decreased exercise tolerance, muscle cramping during strenuous activity, and myoglobinuria. Blood lactate is often very low after exercise, and muscle biopsy shows an excess of normally structured glycogen.

(Choice F) Pyruvate kinase (PK) converts phosphoenolpyruvate to pyruvate during glycolysis. PK deficiency causes chronic hemolytic anemia because glycolysis is the main source of energy for erythrocytes.

Item 2 of 40
Question Id: 1030
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Educational objective:

Glycogen debrancher deficiency (Cori disease) causes accumulation of glycogen with abnormally short outer chains (limit dextrins) due to the inability to degrade branch points. Patients have hypoglycemia, ketoacidosis, hepatomegaly, muscle weakness, and hypotonia.

Biochemistry	Biochemistry (General Principles)	Glycogen storage disease
Subject	System	Topic

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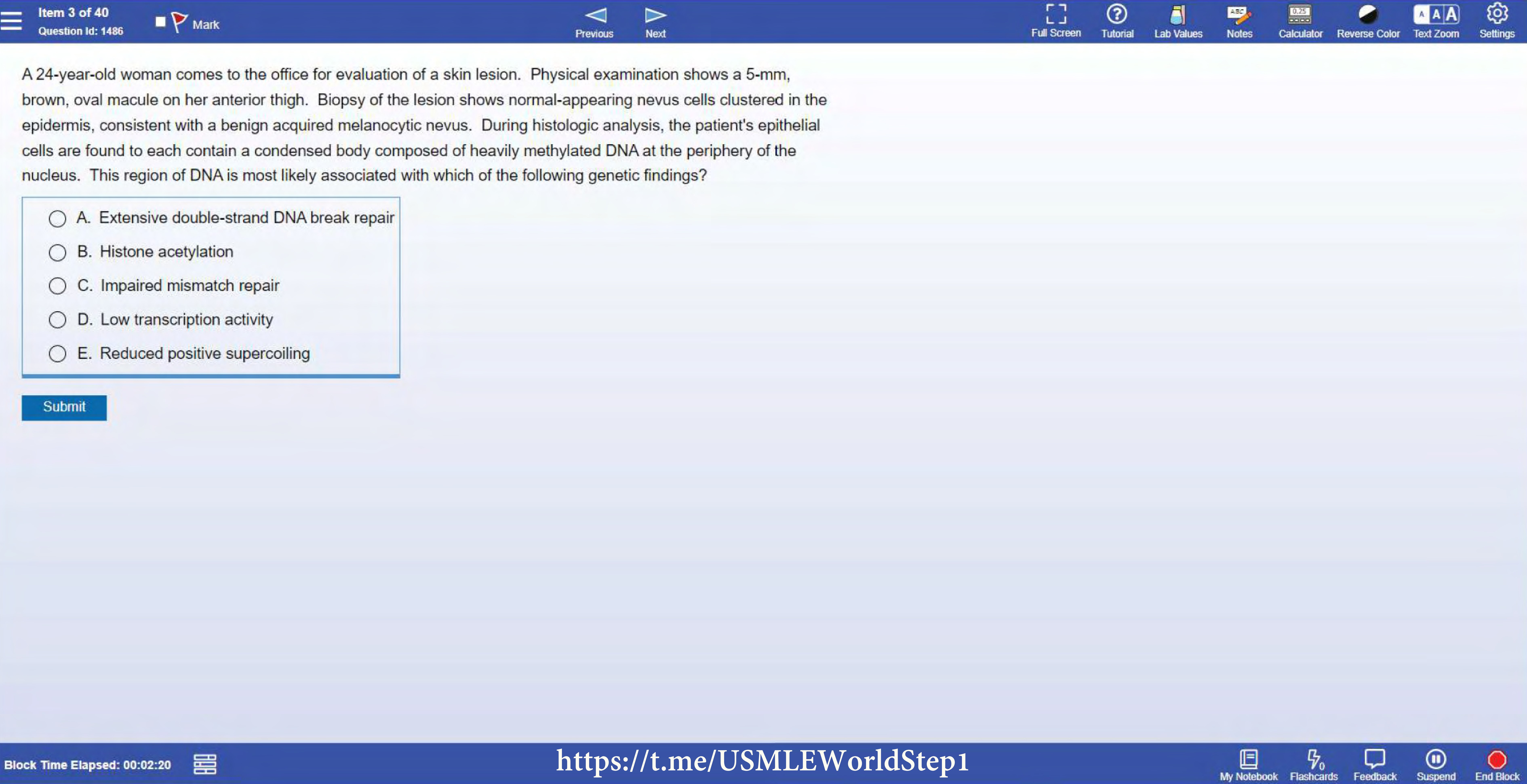
Item 3 of 40
Question Id: 1486
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 24-year-old woman comes to the office for evaluation of a skin lesion. Physical examination shows a 5-mm, brown, oval macule on her anterior thigh. Biopsy of the lesion shows normal-appearing nevus cells clustered in the epidermis, consistent with a benign acquired melanocytic nevus. During histologic analysis, the patient's epithelial cells are found to each contain a condensed body composed of heavily methylated DNA at the periphery of the nucleus. This region of DNA is most likely associated with which of the following genetic findings?

- ○ A. Extensive double-strand DNA break repair
- ○ B. Histone acetylation
- ○ C. Impaired mismatch repair
- ○ D. Low transcription activity
- ○ E. Reduced positive supercoiling

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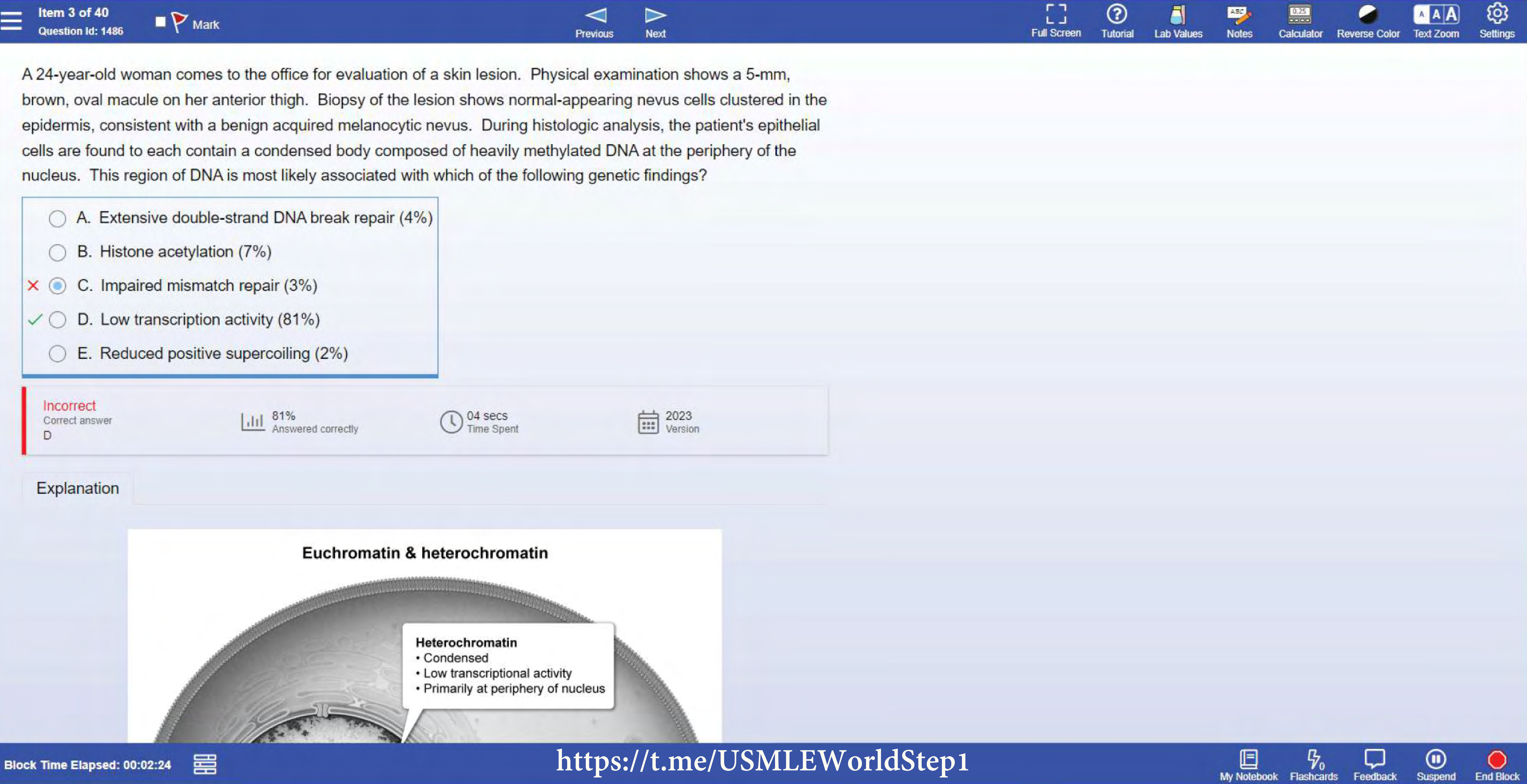
Item 3 of 40
Question Id: 1486
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ A. Extensive double-strand DNA break repair (4%)

○ B. Histone acetylation (7%)

✗ ● C. Impaired mismatch repair (3%)

✓ ○ D. Low transcription activity (81%)

○ E. Reduced positive supercoiling (2%)

Incorrect
Correct answer
D

81%
Answered correctly

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2023
Version

Explanation

Euchromatin & heterochromatin

Heterochromatin
- Condensed
- Low transcriptional activity
- Primarily at periphery of nucleus

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My Notebook
Flashcards
Feedback
Suspend
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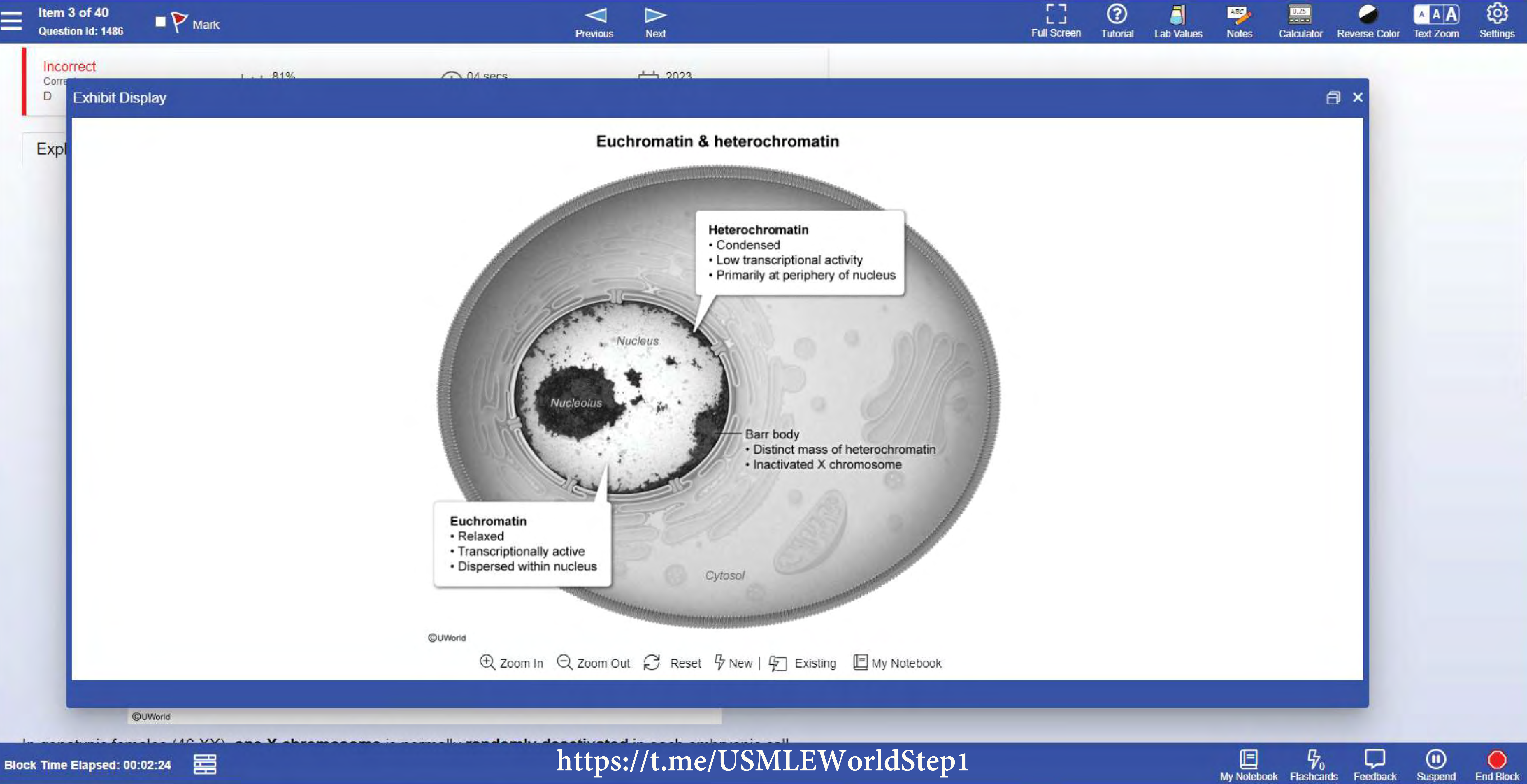
Item 3 of 40
Question Id: 1486
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
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Zoom Out
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New
Existing
My Notebook
Block Time Elapsed: 00:02:24
My Notebook
Flashcards
Feedback
Suspend
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Expl

Euchromatin & heterochromatin

Nucleus
Nucleolus
Cytosol

Heterochromatin
- Condensed
- Low transcriptional activity
- Primarily at periphery of nucleus

Barr body
- Distinct mass of heterochromatin
- Inactivated X chromosome

Euchromatin
- Relaxed
- Transcriptionally active
- Dispersed within nucleus

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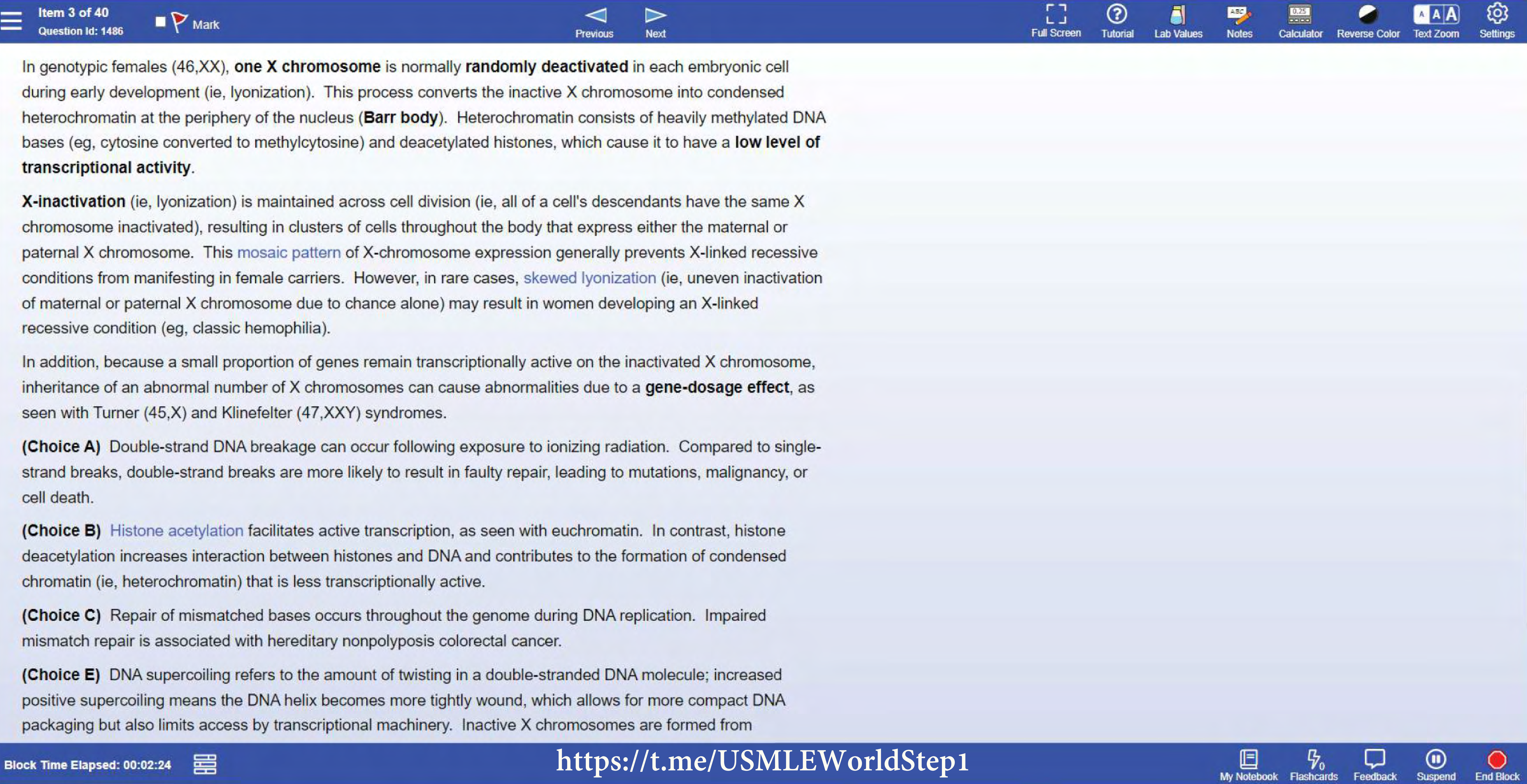
In genotypic females (46,XX), **one X chromosome** is normally **randomly deactivated** in each embryonic cell



In genotypic females (46,XX), **one X chromosome** is normally **randomly deactivated** in each embryonic cell during early development (ie, lyonization). This process converts the inactive X chromosome into condensed heterochromatin at the periphery of the nucleus (**Barr body**). Heterochromatin consists of heavily methylated DNA bases (eg, cytosine converted to methylcytosine) and deacetylated histones, which cause it to have a **low level of transcriptional activity**.

X-inactivation (ie, lyonization) is maintained across cell division (ie, all of a cell's descendants have the same X chromosome inactivated), resulting in clusters of cells throughout the body that express either the maternal or paternal X chromosome. This mosaic pattern of X-chromosome expression generally prevents X-linked recessive conditions from manifesting in female carriers. However, in rare cases, skewed lyonization (ie, uneven inactivation of maternal or paternal X chromosome due to chance alone) may result in women developing an X-linked recessive condition (eg, classic hemophilia).

In addition, because a small proportion of genes remain transcriptionally active on the inactivated X chromosome, inheritance of an abnormal number of X chromosomes can cause abnormalities due to a **gene-dosage effect**, as seen with Turner (45,X) and Klinefelter (47,XXY) syndromes.

(Choice A) Double-strand DNA breakage can occur following exposure to ionizing radiation. Compared to single-strand breaks, double-strand breaks are more likely to result in faulty repair, leading to mutations, malignancy, or cell death.

(Choice B) Histone acetylation facilitates active transcription, as seen with euchromatin. In contrast, histone deacetylation increases interaction between histones and DNA and contributes to the formation of condensed chromatin (ie, heterochromatin) that is less transcriptionally active.

(Choice C) Repair of mismatched bases occurs throughout the genome during DNA replication. Impaired mismatch repair is associated with hereditary nonpolyposis colorectal cancer.

(Choice E) DNA supercoiling refers to the amount of twisting in a double-stranded DNA molecule; increased positive supercoiling means the DNA helix becomes more tightly wound, which allows for more compact DNA packaging but also limits access by transcriptional machinery. Inactive X chromosomes are formed from

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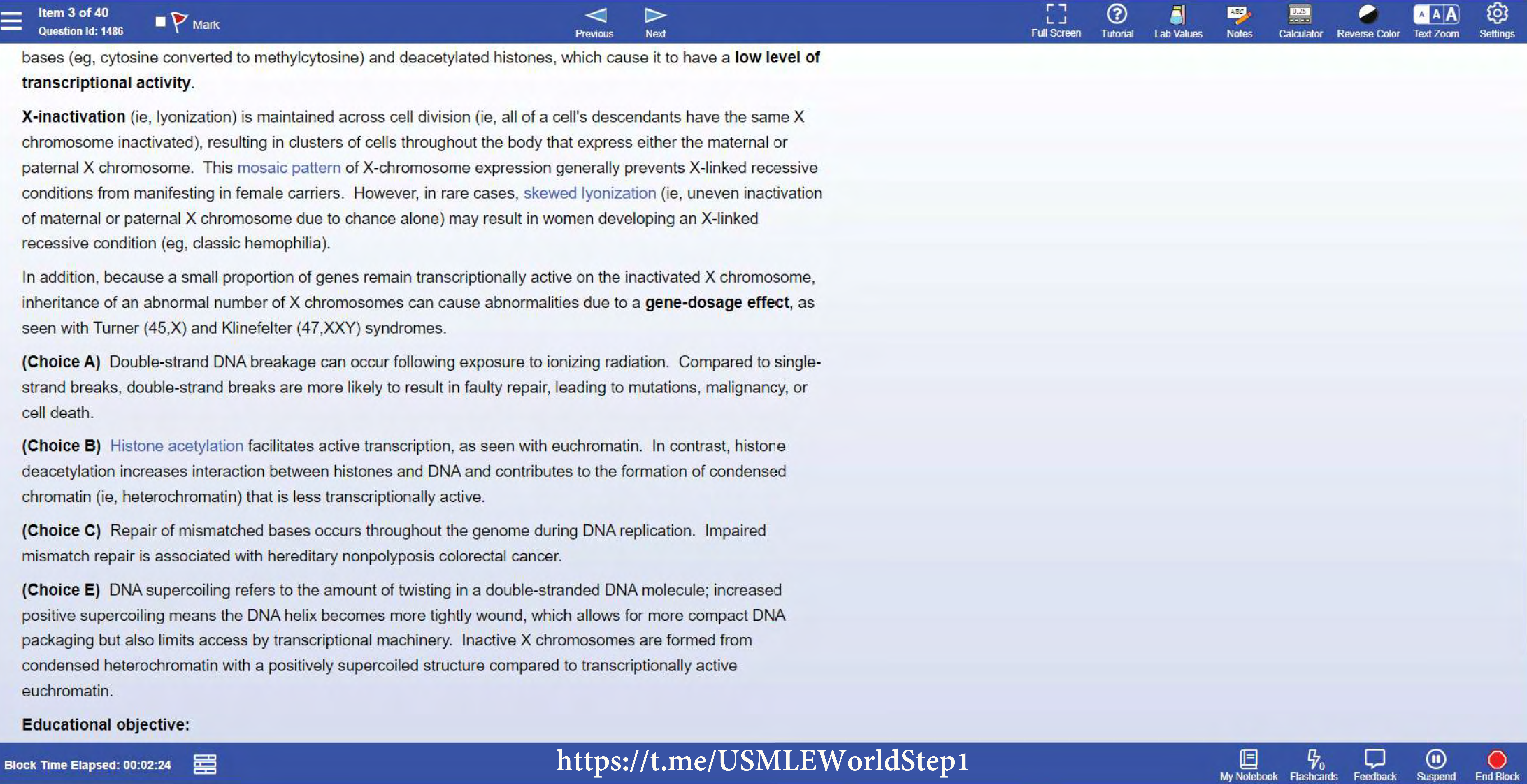


bases (eg, cytosine converted to methylcytosine) and deacetylated histones, which cause it to have a **low level of transcriptional activity**.

X-inactivation (ie, lyonization) is maintained across cell division (ie, all of a cell's descendants have the same X chromosome inactivated), resulting in clusters of cells throughout the body that express either the maternal or paternal X chromosome. This mosaic pattern of X-chromosome expression generally prevents X-linked recessive conditions from manifesting in female carriers. However, in rare cases, skewed lyonization (ie, uneven inactivation of maternal or paternal X chromosome due to chance alone) may result in women developing an X-linked recessive condition (eg, classic hemophilia).

In addition, because a small proportion of genes remain transcriptionally active on the inactivated X chromosome, inheritance of an abnormal number of X chromosomes can cause abnormalities due to a **gene-dosage effect**, as seen with Turner (45,X) and Klinefelter (47,XXY) syndromes.

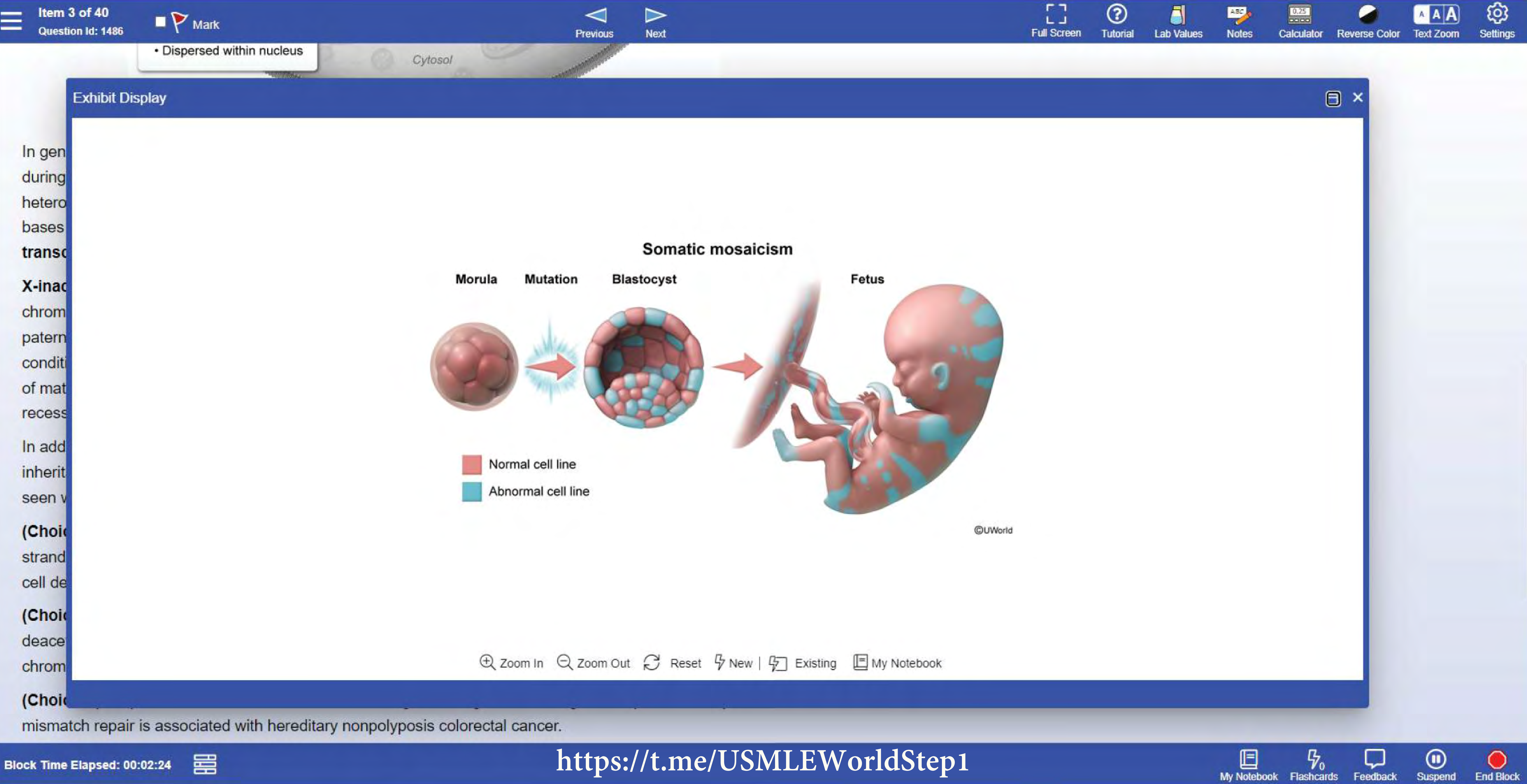
(Choice A) Double-strand DNA breakage can occur following exposure to ionizing radiation. Compared to single-strand breaks, double-strand breaks are more likely to result in faulty repair, leading to mutations, malignancy, or cell death.

(Choice B) Histone acetylation facilitates active transcription, as seen with euchromatin. In contrast, histone deacetylation increases interaction between histones and DNA and contributes to the formation of condensed chromatin (ie, heterochromatin) that is less transcriptionally active.

(Choice C) Repair of mismatched bases occurs throughout the genome during DNA replication. Impaired mismatch repair is associated with hereditary nonpolyposis colorectal cancer.

(Choice E) DNA supercoiling refers to the amount of twisting in a double-stranded DNA molecule; increased positive supercoiling means the DNA helix becomes more tightly wound, which allows for more compact DNA packaging but also limits access by transcriptional machinery. Inactive X chromosomes are formed from condensed heterochromatin with a positively supercoiled structure compared to transcriptionally active euchromatin.

Educational objective:


Item 3 of 40
Question Id: 1486
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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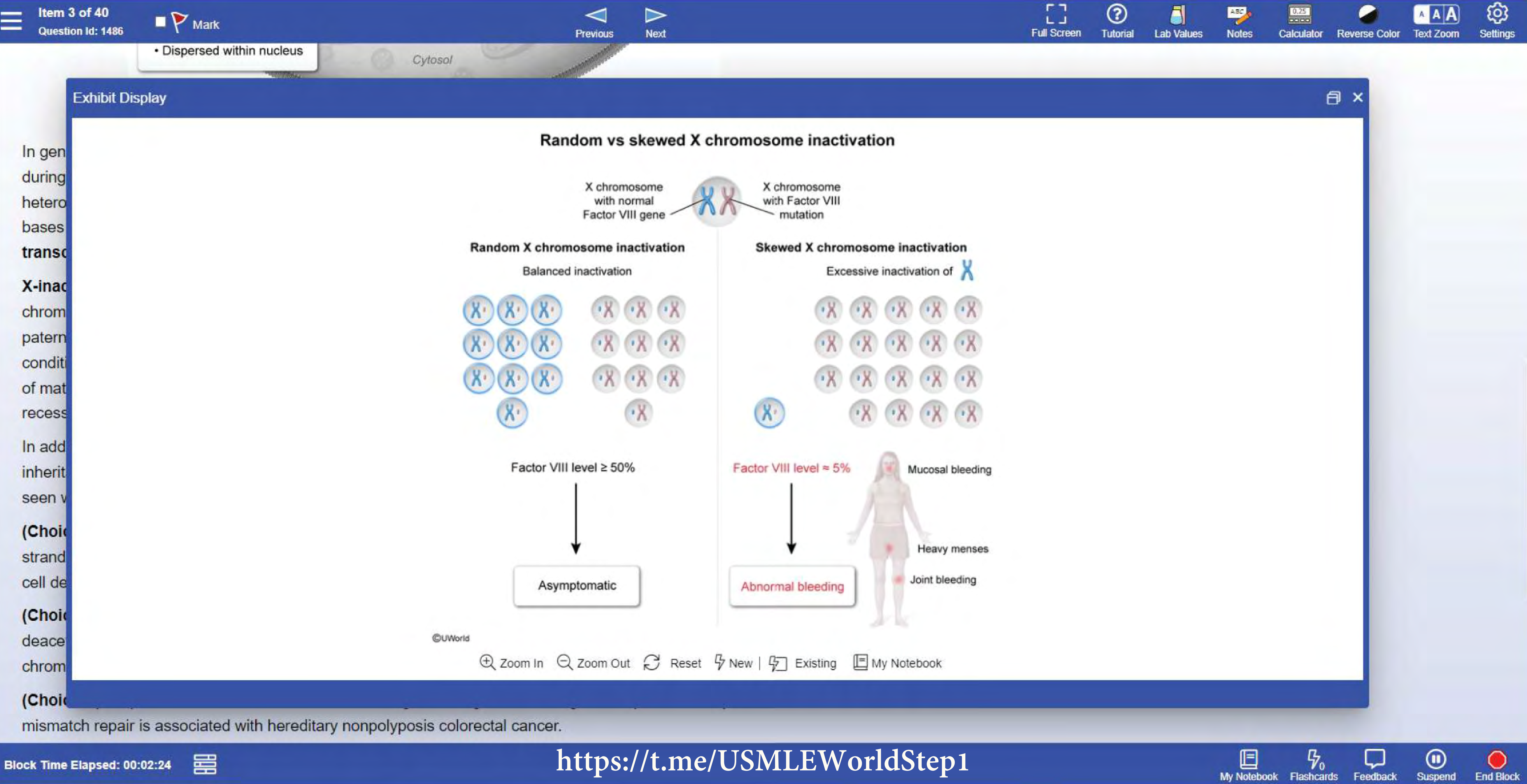
Item 3 of 40
Question Id: 1486
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Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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Exhibit Display

Random vs skewed X chromosome inactivation

X chromosome with normal Factor VIII gene
X chromosome with Factor VIII mutation
Random X chromosome inactivation
Balanced inactivation
Skewed X chromosome inactivation
Excessive inactivation of X
Factor VIII level ≥ 50%
Asymptomatic
Factor VIII level ≈ 5%
Abnormal bleeding
Mucosal bleeding
Heavy menses
Joint bleeding

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chromosome inactivated), resulting in clusters of cells throughout the body that express either the maternal or

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composed of heavily methylated DNA and deacetylated histones, causing it to have a low level of transcriptional

activity

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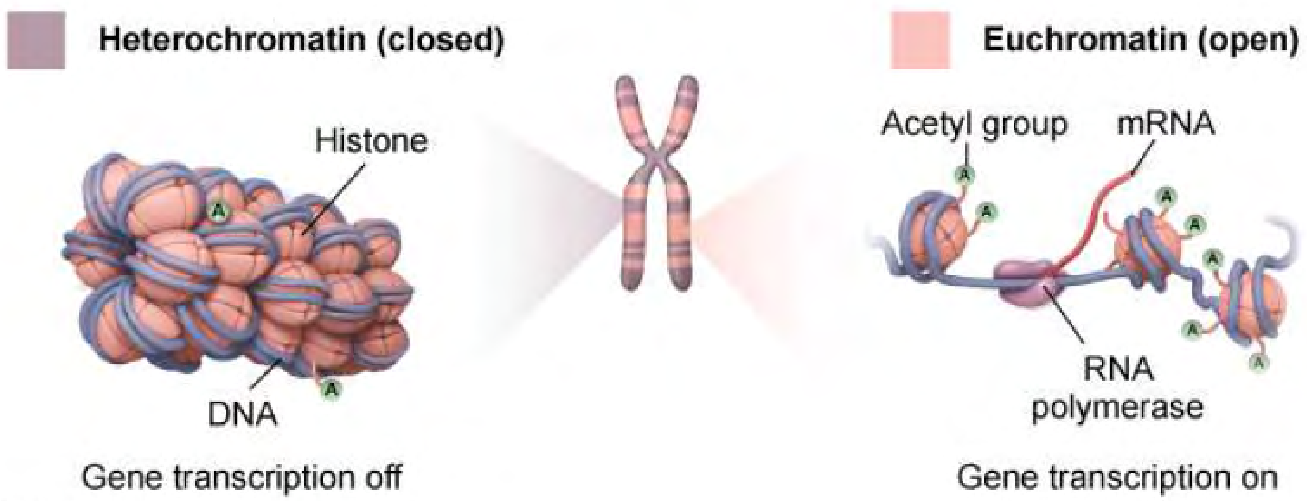
▨ Heterochromatin (closed)
Histone
A
DNA
Gene transcription off
▨ Euchromatin (open)
Acetyl group
mRNA
RNA polymerase
Gene transcription on

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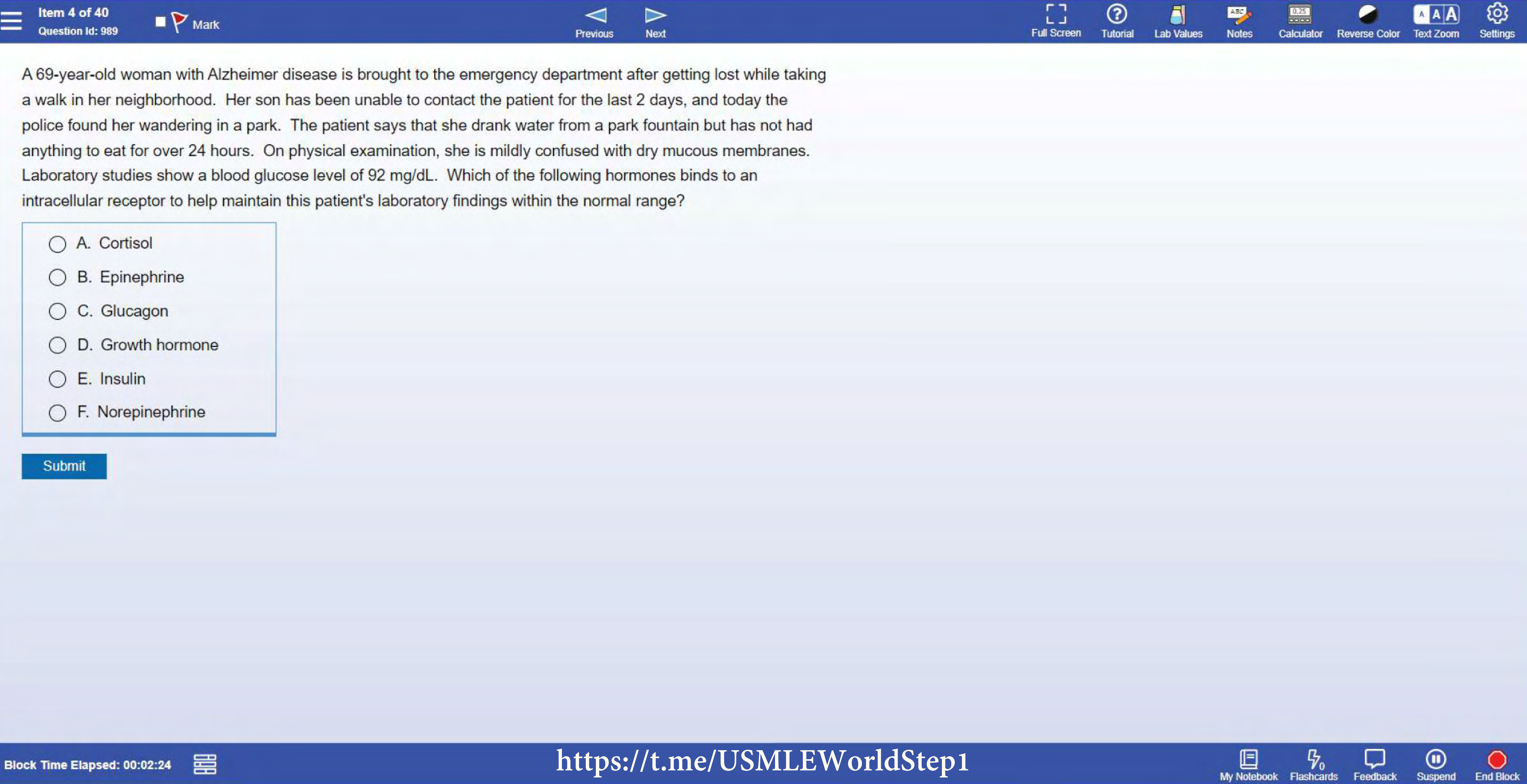
Item 4 of 40
Question Id: 989
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 69-year-old woman with Alzheimer disease is brought to the emergency department after getting lost while taking a walk in her neighborhood. Her son has been unable to contact the patient for the last 2 days, and today the police found her wandering in a park. The patient says that she drank water from a park fountain but has not had anything to eat for over 24 hours. On physical examination, she is mildly confused with dry mucous membranes. Laboratory studies show a blood glucose level of 92 mg/dL. Which of the following hormones binds to an intracellular receptor to help maintain this patient's laboratory findings within the normal range?

- ○ A. Cortisol
- ○ B. Epinephrine
- ○ C. Glucagon
- ○ D. Growth hormone
- ○ E. Insulin
- ○ F. Norepinephrine

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A 69-year-old woman with Alzheimer disease is brought to the emergency department after getting lost while taking a walk in her neighborhood. Her son has been unable to contact the patient for the last 2 days, and today the police found her wandering in a park. The patient says that she drank water from a park fountain but has not had anything to eat for over 24 hours. On physical examination, she is mildly confused with dry mucous membranes. Laboratory studies show a blood glucose level of 92 mg/dL. Which of the following hormones binds to an intracellular receptor to help maintain this patient's laboratory findings within the normal range?

- ✓ ○ A. Cortisol (64%)
- ○ B. Epinephrine (3%)
- ○ C. Glucagon (26%)
- ✗ ● D. Growth hormone (2%)
- ○ E. Insulin (2%)
- ○ F. Norepinephrine (0%)

Incorrect
Correct answer
A

64%
Answered correctly

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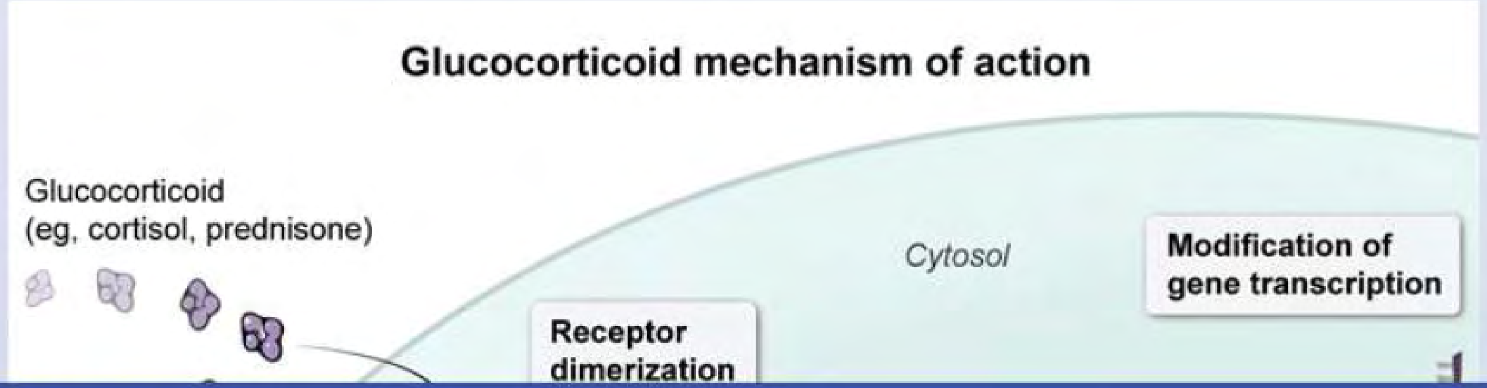
Explanation



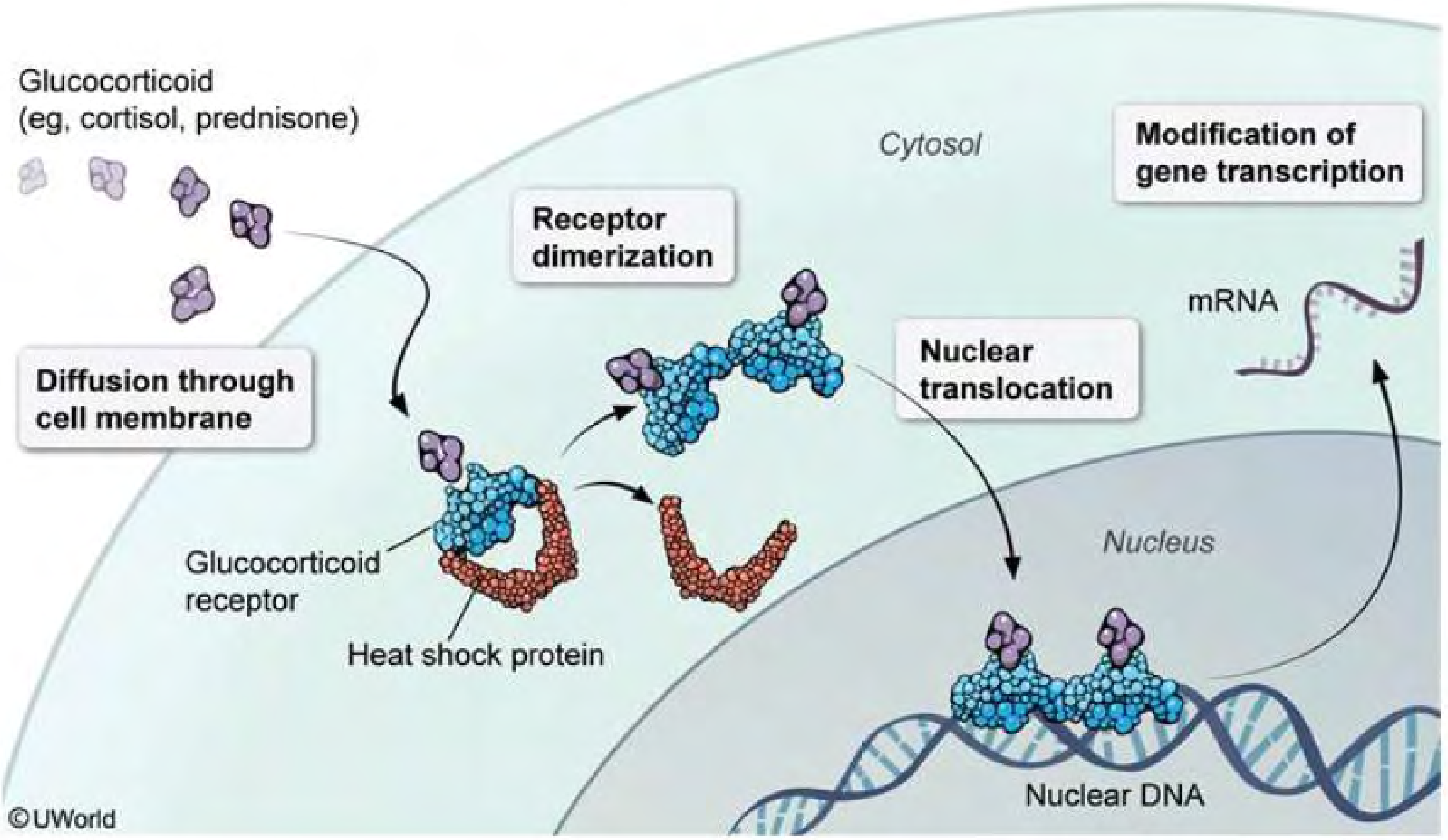
Glucocorticoid mechanism of action

Glucocorticoid
(eg, cortisol, prednisone)
Cytosol
Modification of gene transcription
Receptor dimerization

Glucocorticoid

Exhibit Display

Glucocorticoid mechanism of action


Glucocorticoid
(eg, cortisol, prednisone)
Cytosol
Modification of gene transcription
Receptor dimerization
mRNA
Nuclear translocation
Diffusion through cell membrane
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Heat shock protein
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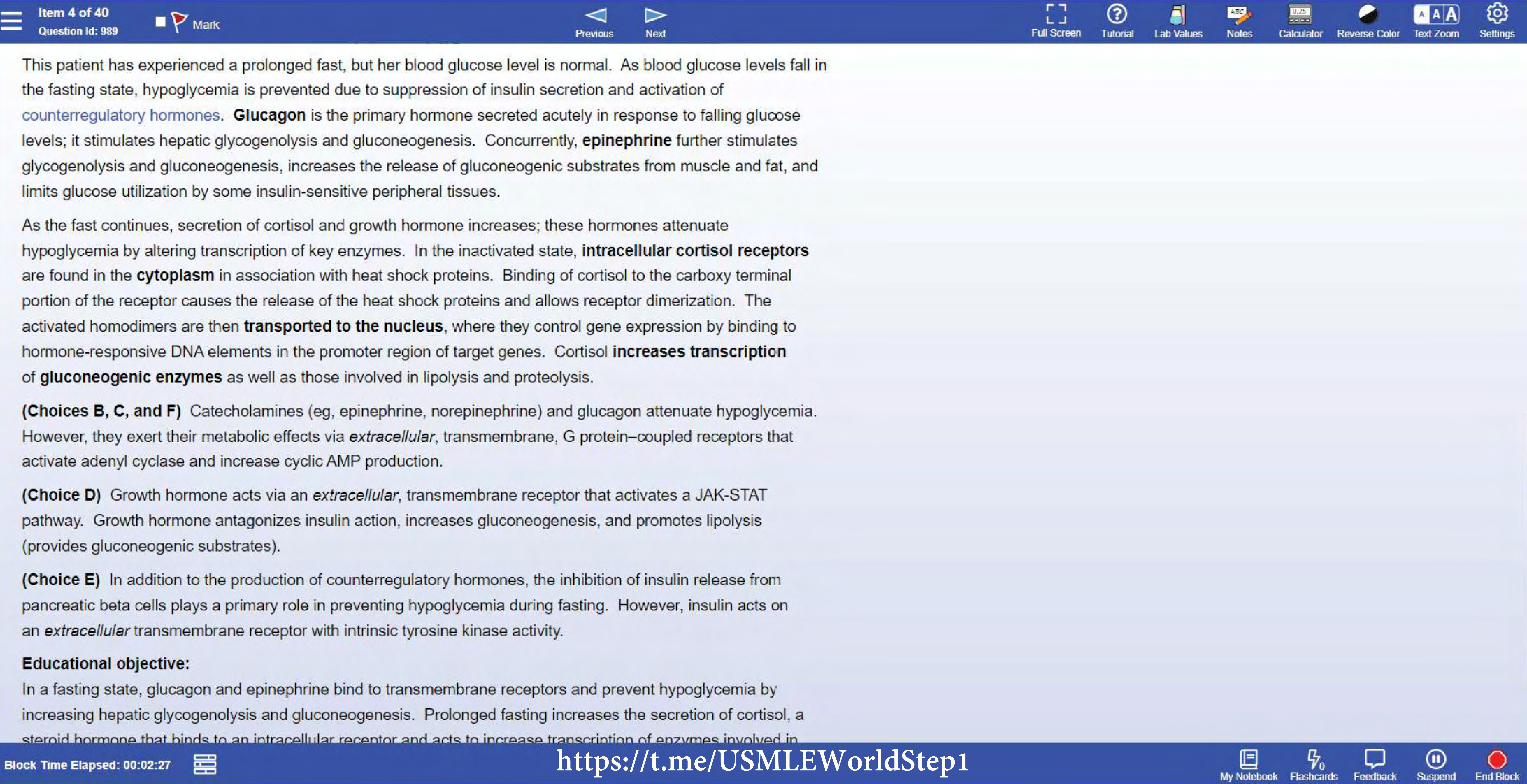
of **gluconeogenic enzymes** as well as those involved in lipolysis and proteolysis.



This patient has experienced a prolonged fast, but her blood glucose level is normal. As blood glucose levels fall in the fasting state, hypoglycemia is prevented due to suppression of insulin secretion and activation of counterregulatory hormones. **Glucagon** is the primary hormone secreted acutely in response to falling glucose levels; it stimulates hepatic glycogenolysis and gluconeogenesis. Concurrently, **epinephrine** further stimulates glycogenolysis and gluconeogenesis, increases the release of gluconeogenic substrates from muscle and fat, and limits glucose utilization by some insulin-sensitive peripheral tissues.

As the fast continues, secretion of cortisol and growth hormone increases; these hormones attenuate hypoglycemia by altering transcription of key enzymes. In the inactivated state, **intracellular cortisol receptors** are found in the **cytoplasm** in association with heat shock proteins. Binding of cortisol to the carboxy terminal portion of the receptor causes the release of the heat shock proteins and allows receptor dimerization. The activated homodimers are then **transported to the nucleus**, where they control gene expression by binding to hormone-responsive DNA elements in the promoter region of target genes. Cortisol **increases transcription** of **gluconeogenic enzymes** as well as those involved in lipolysis and proteolysis.

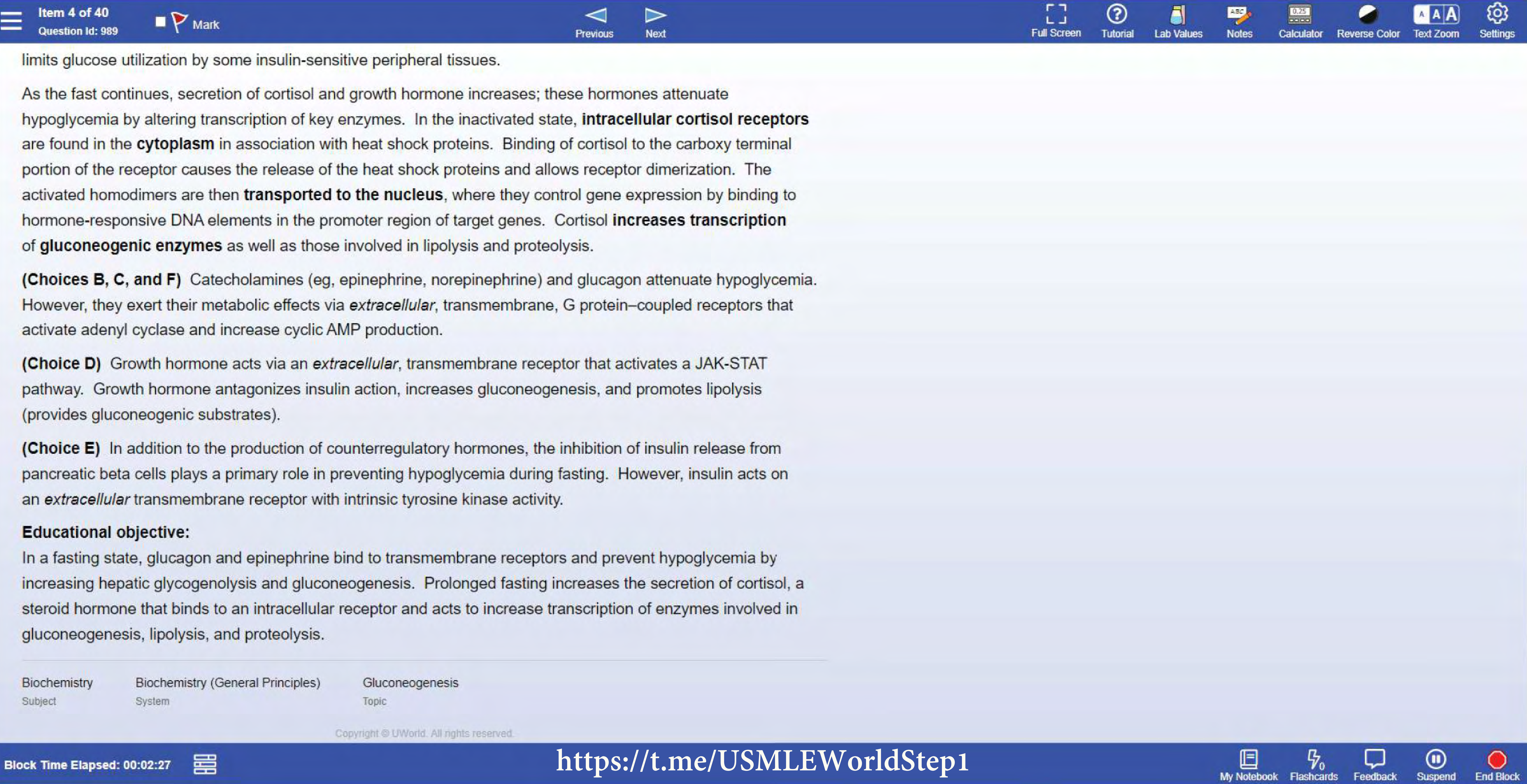
(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate hypoglycemia. However, they exert their metabolic effects via *extracellular*, transmembrane, G protein–coupled receptors that activate adenyl cyclase and increase cyclic AMP production.

(Choice D) Growth hormone acts via an *extracellular*, transmembrane receptor that activates a JAK-STAT pathway. Growth hormone antagonizes insulin action, increases gluconeogenesis, and promotes lipolysis (provides gluconeogenic substrates).

(Choice E) In addition to the production of counterregulatory hormones, the inhibition of insulin release from pancreatic beta cells plays a primary role in preventing hypoglycemia during fasting. However, insulin acts on an *extracellular* transmembrane receptor with intrinsic tyrosine kinase activity.

Educational objective:

In a fasting state, glucagon and epinephrine bind to transmembrane receptors and prevent hypoglycemia by increasing hepatic glycogenolysis and gluconeogenesis. Prolonged fasting increases the secretion of cortisol, a steroid hormone that binds to an intracellular receptor and acts to increase transcription of enzymes involved in



limits glucose utilization by some insulin-sensitive peripheral tissues.

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(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate hypoglycemia. However, they exert their metabolic effects via *extracellular*, transmembrane, G protein–coupled receptors that activate adenyl cyclase and increase cyclic AMP production.

(Choice D) Growth hormone acts via an *extracellular*, transmembrane receptor that activates a JAK-STAT pathway. Growth hormone antagonizes insulin action, increases gluconeogenesis, and promotes lipolysis (provides gluconeogenic substrates).

(Choice E) In addition to the production of counterregulatory hormones, the inhibition of insulin release from pancreatic beta cells plays a primary role in preventing hypoglycemia during fasting. However, insulin acts on an *extracellular* transmembrane receptor with intrinsic tyrosine kinase activity.

Educational objective:

In a fasting state, glucagon and epinephrine bind to transmembrane receptors and prevent hypoglycemia by increasing hepatic glycogenolysis and gluconeogenesis. Prolonged fasting increases the secretion of cortisol, a steroid hormone that binds to an intracellular receptor and acts to increase transcription of enzymes involved in gluconeogenesis, lipolysis, and proteolysis.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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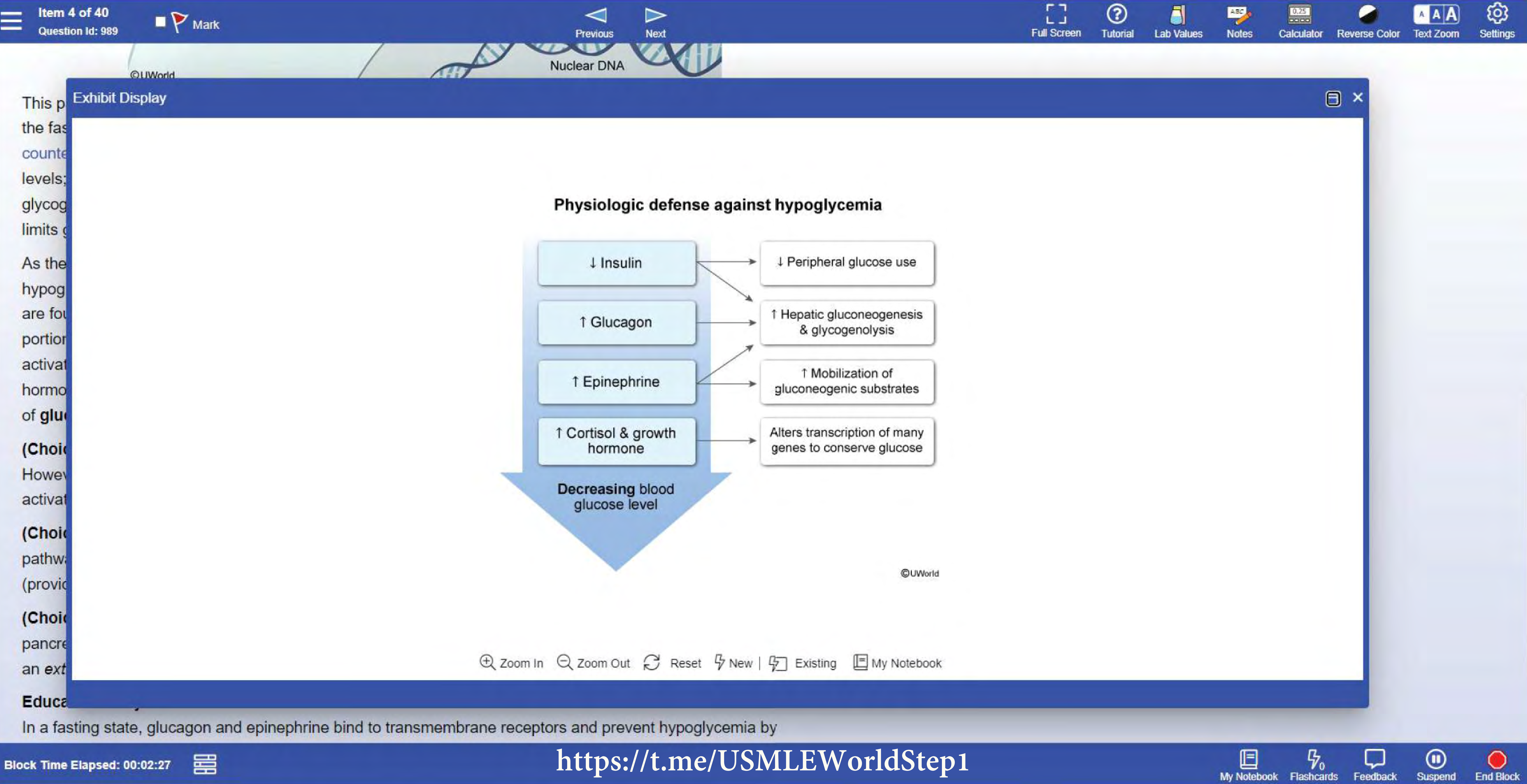
Item 4 of 40
Question Id: 989
Mark
Previous
Next
Full Screen
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Lab Values
Notes
Calculator
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My Notebook
Flashcards
Feedback
Suspend
End Block

Physiologic defense against hypoglycemia

↓ Insulin	↓ Peripheral glucose use
↑ Glucagon	↑ Hepatic gluconeogenesis & glycogenolysis
↑ Epinephrine	↑ Mobilization of gluconeogenic substrates
↑ Cortisol & growth hormone	Alters transcription of many genes to conserve glucose

Decreasing blood glucose level

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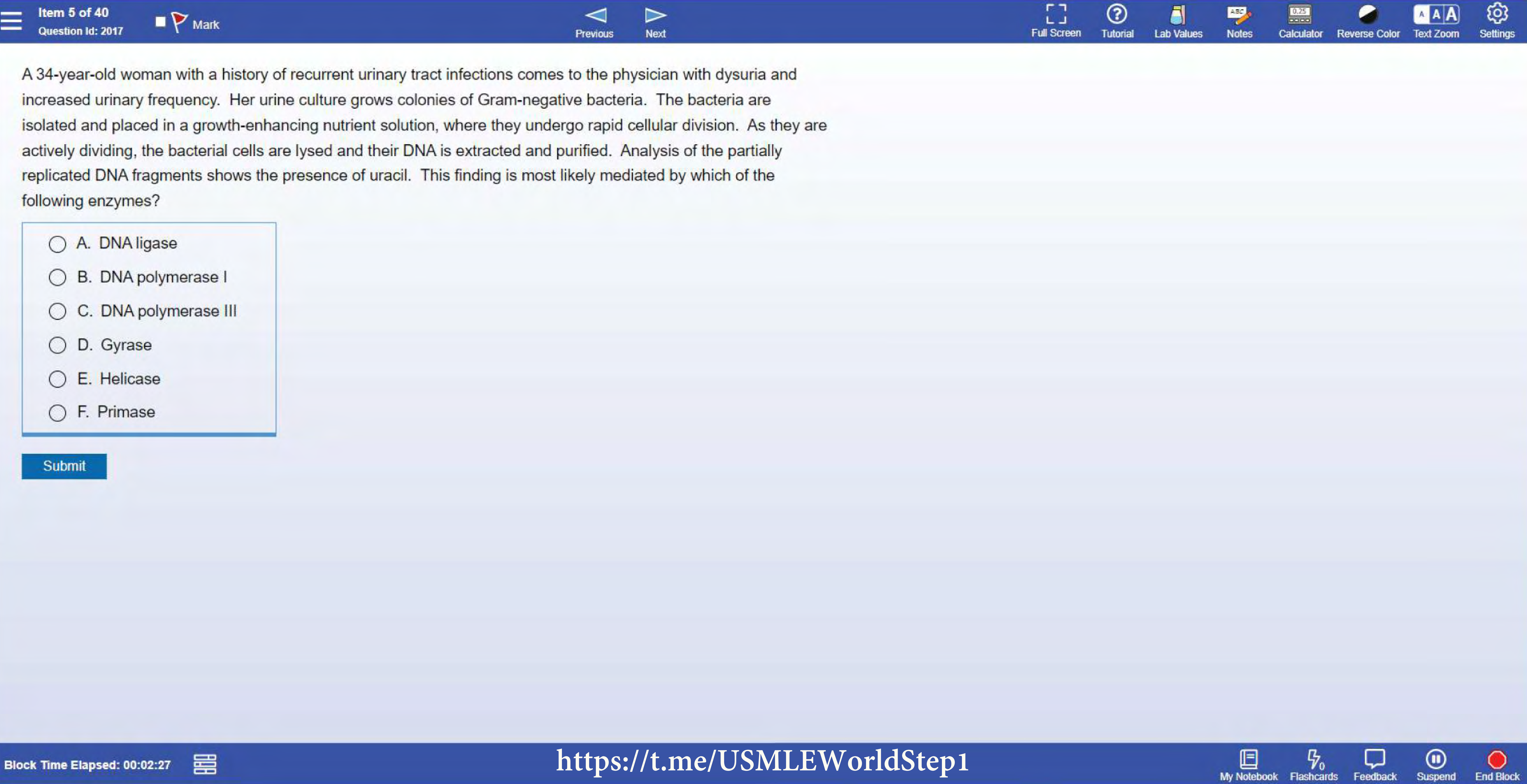
Educa

In a fasting state, glucagon and epinephrine bind to transmembrane receptors and prevent hypoglycemia by


Item 5 of 40
Question Id: 2017
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:02:27
My Notebook
Flashcards
Feedback
Suspend
End Block

A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

○ A. DNA ligase
○ B. DNA polymerase I
○ C. DNA polymerase III
○ D. Gyrase
○ E. Helicase
○ F. Primase

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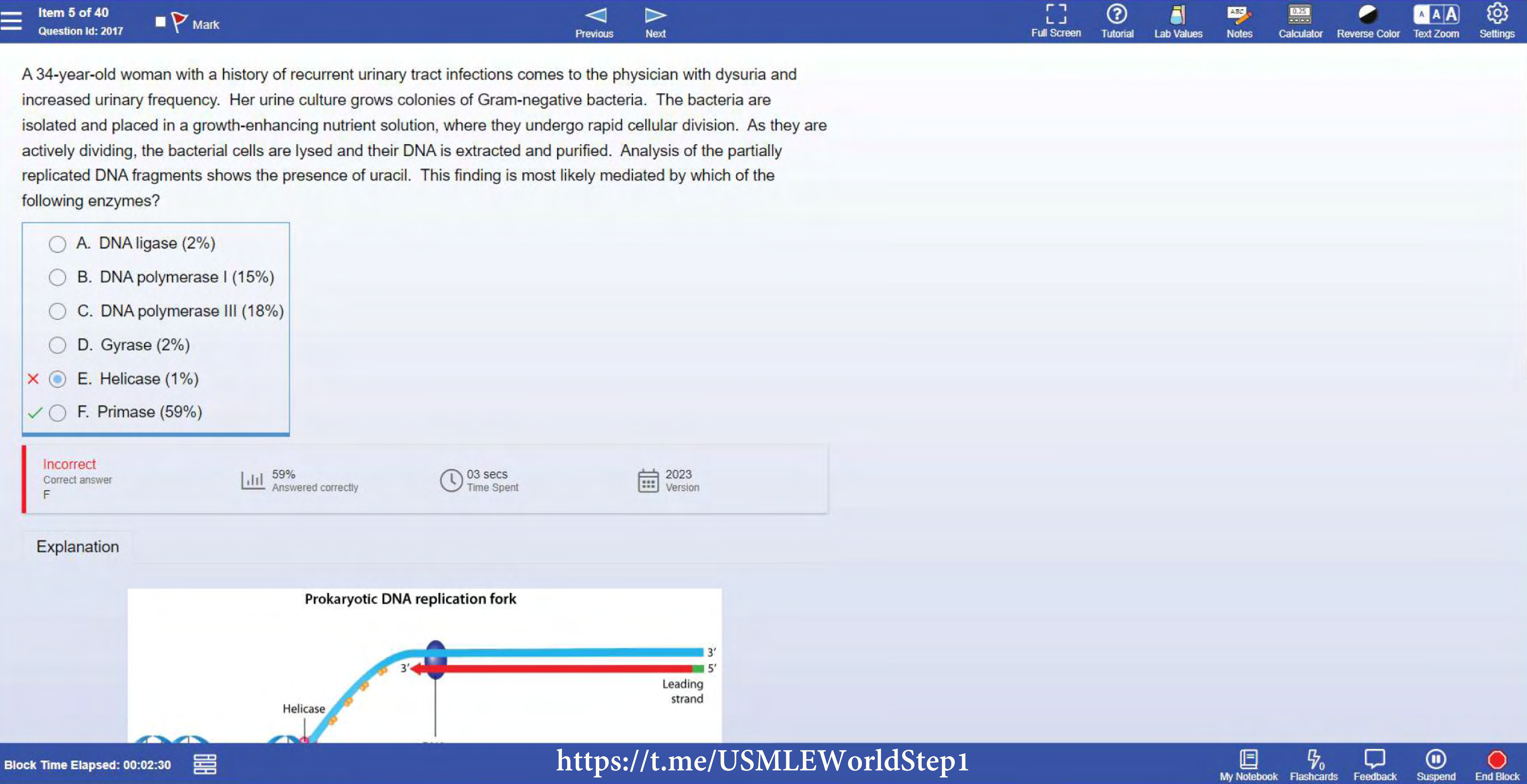
Item 5 of 40
Question Id: 2017
Mark
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Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

○ A. DNA ligase (2%)

○ B. DNA polymerase I (15%)

○ C. DNA polymerase III (18%)

○ D. Gyrase (2%)

✗ ● E. Helicase (1%)

✓ ○ F. Primase (59%)

Incorrect
Correct answer
F

59%
Answered correctly

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2023
Version

Explanation

Prokaryotic DNA replication fork

3′
5′
3′
Leading strand
Helicase

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My Notebook
Flashcards
Feedback
Suspend
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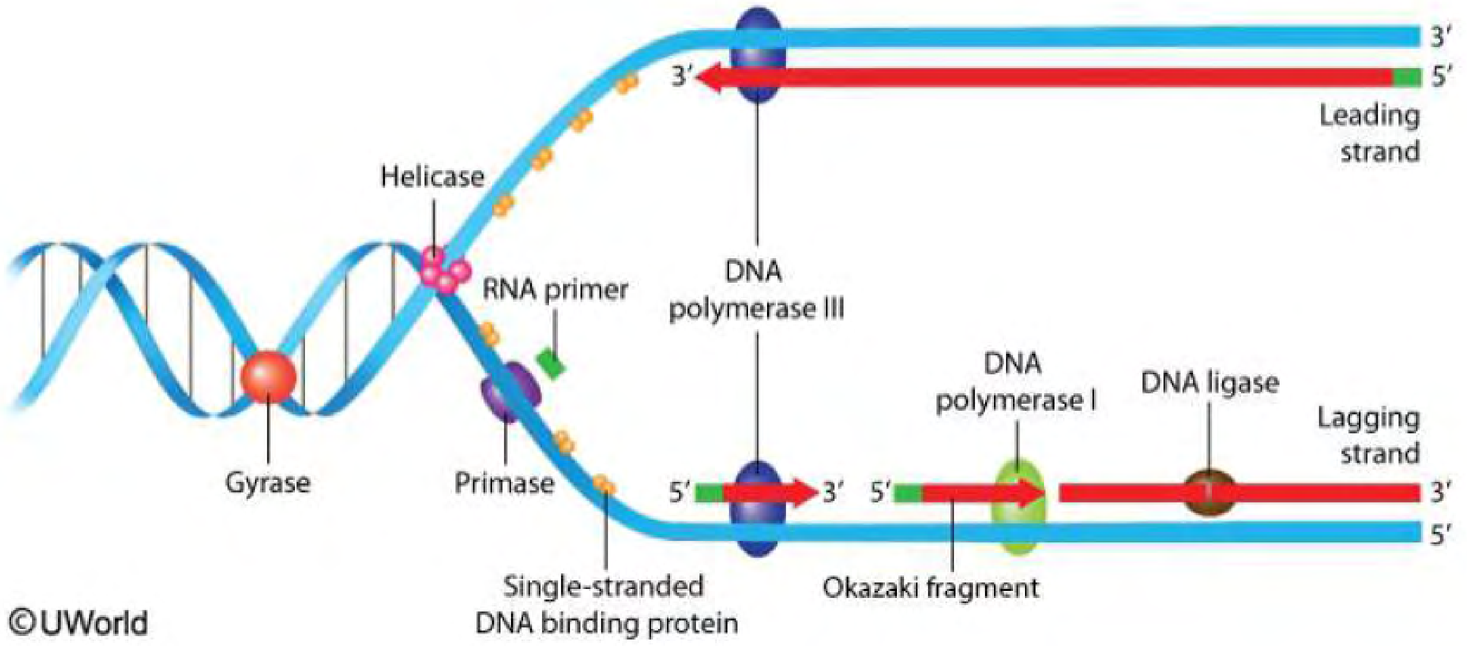
Prokaryotic DNA replication fork


3′
5′
3′
Leading strand
Helicase
RNA primer
DNA polymerase III
DNA polymerase I
DNA ligase
Lagging strand
Gyrase
Primase
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Single-stranded DNA binding protein
Okazaki fragment

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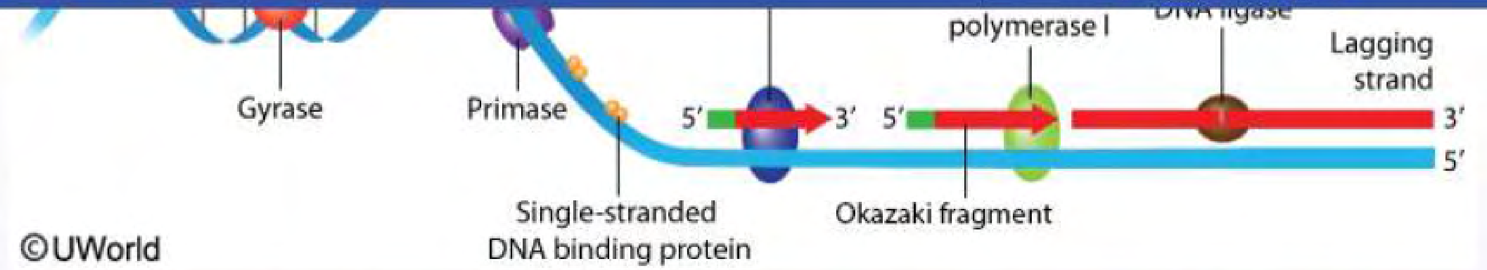
damaged DNA segments. The 3'→ 5' exonuclease activity of DNA polymerase I and III provides a proofreading



This question describes a scenario in which uracil is found in association with bacterial DNA during prokaryotic DNA replication. In general, uracil is found only in RNA, so the question essentially asks which enzyme involved in DNA synthesis catalyzes the formation of RNA strands. In prokaryotic DNA replication, primase (an RNA polymerase) is responsible for synthesizing a short RNA primer using the separated strands of DNA at the replication fork as templates. DNA replication then proceeds, with DNA polymerase using the 3' hydroxyl group of the RNA primer as a starting point for synthesis. Primase is a crucial enzyme for bacterial replication as DNA polymerase cannot initiate DNA synthesis without this short nucleic acid sequence primer.

(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→ 3' exonuclease activity that can remove RNA primers and damaged DNA segments. The 3'→ 5' exonuclease activity of DNA polymerase I and III provides a proofreading function that fixes mismatched nucleotides in the newly formed daughter strands.

(Choices D and E) Helicase unwinds DNA at the replication fork. However, this process results in supercoiling of the DNA. DNA gyrase is a type II topoisomerase that helps to relieve the resultant strain.

Educational objective:

Primase is a DNA-dependent RNA polymerase that incorporates short RNA primers into replicating DNA.

Biochemistry	Genetics (General Principles)	Transcription
Subject	System	Topic

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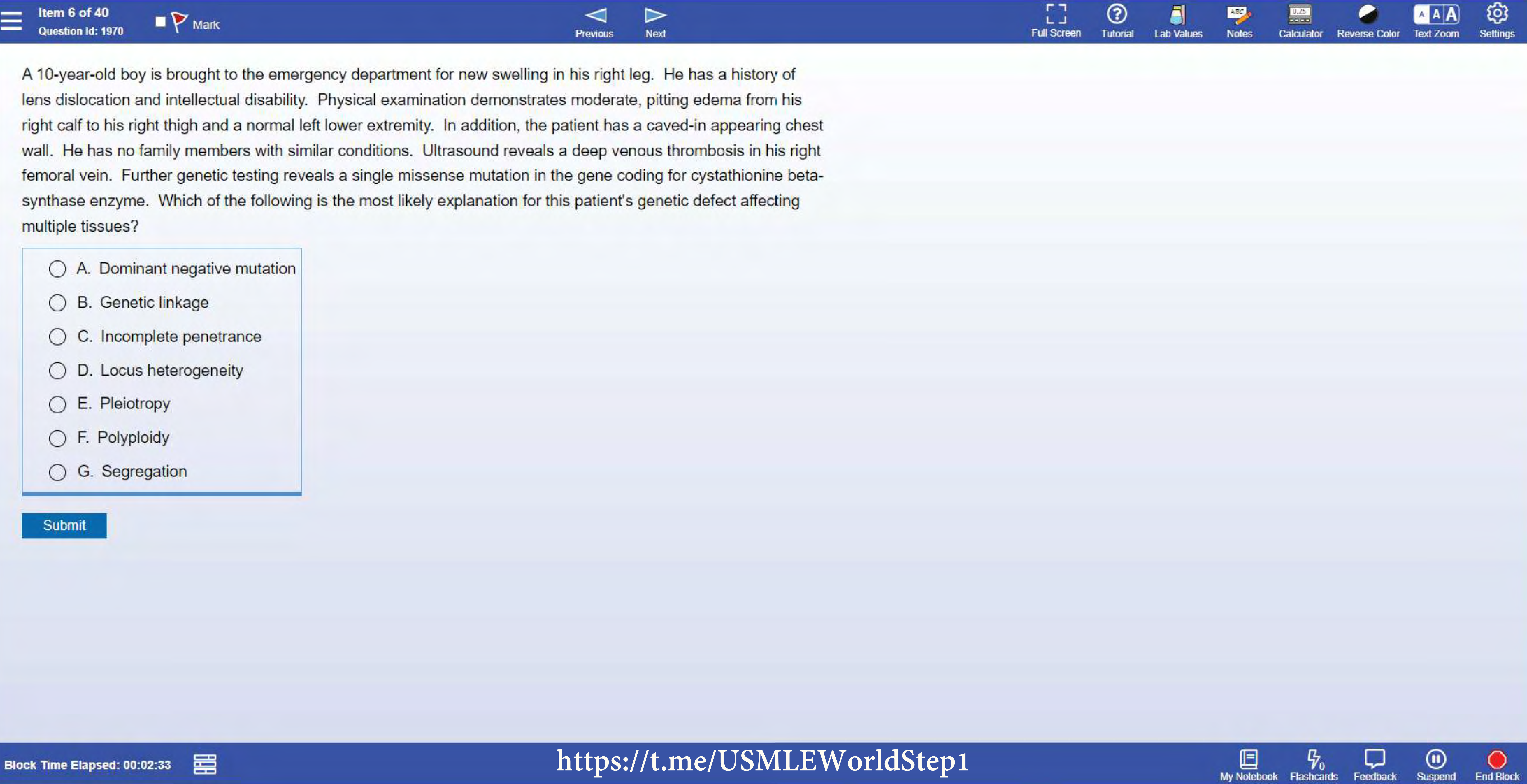
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Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 6 of 40
Question Id: 1970

A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

○ A. Dominant negative mutation
○ B. Genetic linkage
○ C. Incomplete penetrance
○ D. Locus heterogeneity
○ E. Pleiotropy
○ F. Polyploidy
○ G. Segregation

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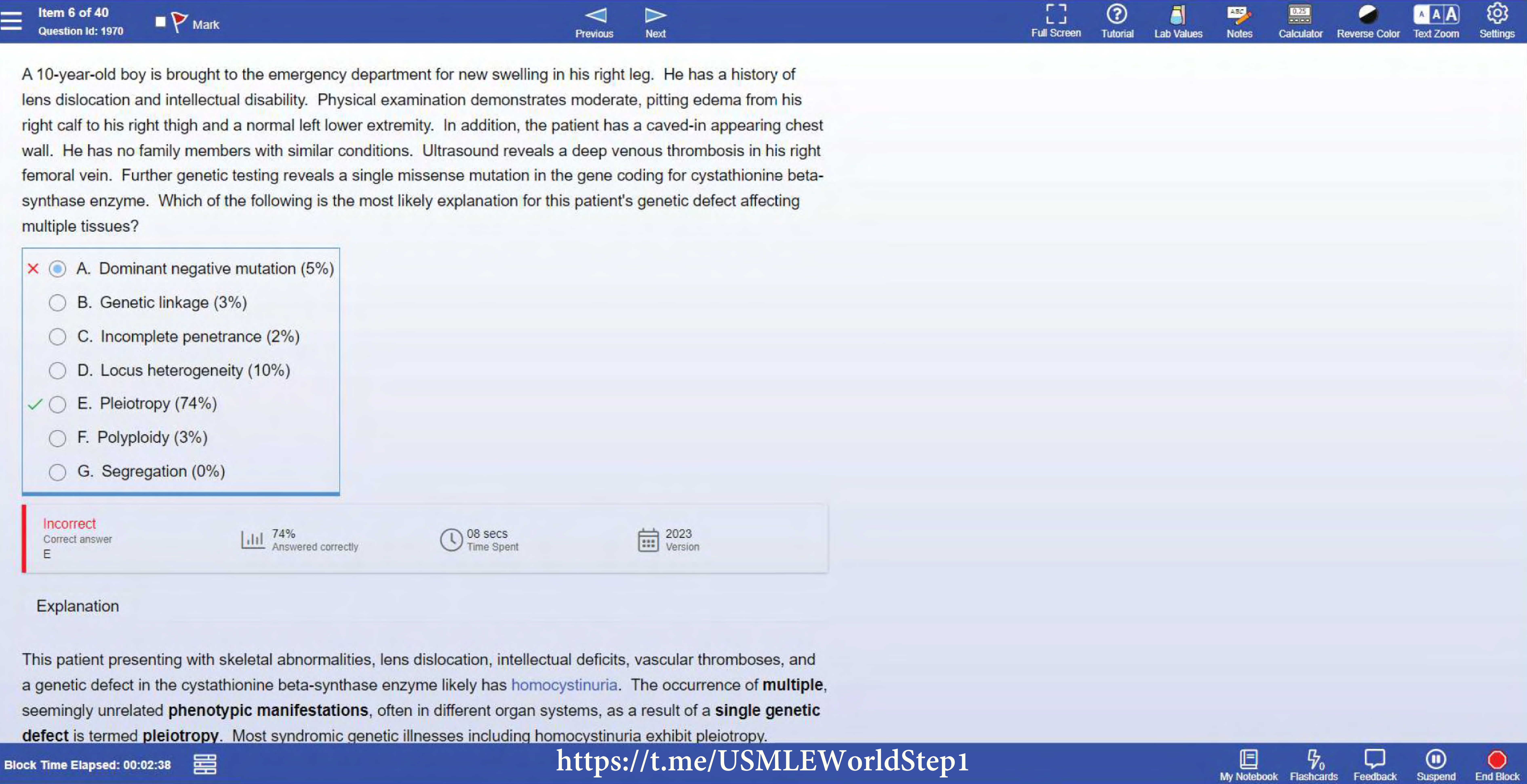
Item 6 of 40
Question Id: 1970
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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My Notebook
Flashcards
Feedback
Suspend
End Block

A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- ✗ ● A. Dominant negative mutation (5%)
- ○ B. Genetic linkage (3%)
- ○ C. Incomplete penetrance (2%)
- ○ D. Locus heterogeneity (10%)
- ✓ ○ E. Pleiotropy (74%)
- ○ F. Polyploidy (3%)
- ○ G. Segregation (0%)

Incorrect
Correct answer
E

74%
Answered correctly

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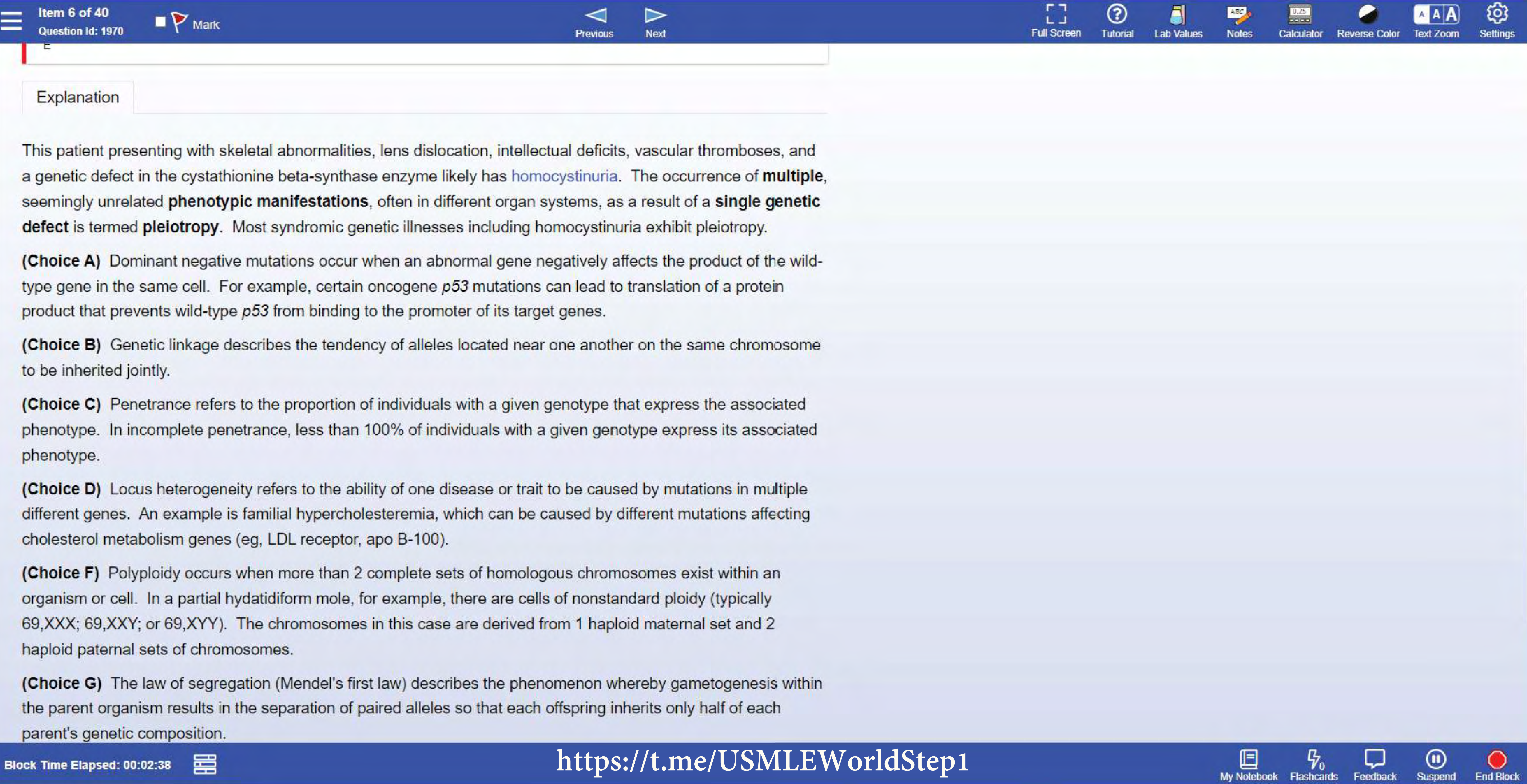
Version

Explanation

This patient presenting with skeletal abnormalities, lens dislocation, intellectual deficits, vascular thromboses, and a genetic defect in the cystathionine beta-synthase enzyme likely has homocystinuria. The occurrence of **multiple**, seemingly unrelated **phenotypic manifestations**, often in different organ systems, as a result of a **single genetic defect** is termed **pleiotropy**. Most syndromic genetic illnesses including homocystinuria exhibit pleiotropy.



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(Choice A) Dominant negative mutations occur when an abnormal gene negatively affects the product of the wild-type gene in the same cell. For example, certain oncogene *p53* mutations can lead to translation of a protein product that prevents wild-type *p53* from binding to the promoter of its target genes.

(Choice B) Genetic linkage describes the tendency of alleles located near one another on the same chromosome to be inherited jointly.

(Choice C) Penetrance refers to the proportion of individuals with a given genotype that express the associated phenotype. In incomplete penetrance, less than 100% of individuals with a given genotype express its associated phenotype.

(Choice D) Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesteremia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor, apo B-100).

(Choice F) Polyploidy occurs when more than 2 complete sets of homologous chromosomes exist within an organism or cell. In a partial hydatidiform mole, for example, there are cells of nonstandard ploidy (typically 69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes.

(Choice G) The law of segregation (Mendel's first law) describes the phenomenon whereby gametogenesis within the parent organism results in the separation of paired alleles so that each offspring inherits only half of each parent's genetic composition.

Item 6 of 40
Question Id: 1970
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

product that prevents wild-type *p53* from binding to the promoter of its target genes.

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Educational objective:

Pleiotropy describes instances where multiple phenotypic manifestations result from a single genetic mutation. Most syndromic genetic illnesses exhibit pleiotropy.

References

- Pleiotropy in complex traits: challenges and strategies.

Genetics	Genetics (General Principles)	Pleiotropy
Subject	System	Topic

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My Notebook
Flashcards
Feedback
Suspend
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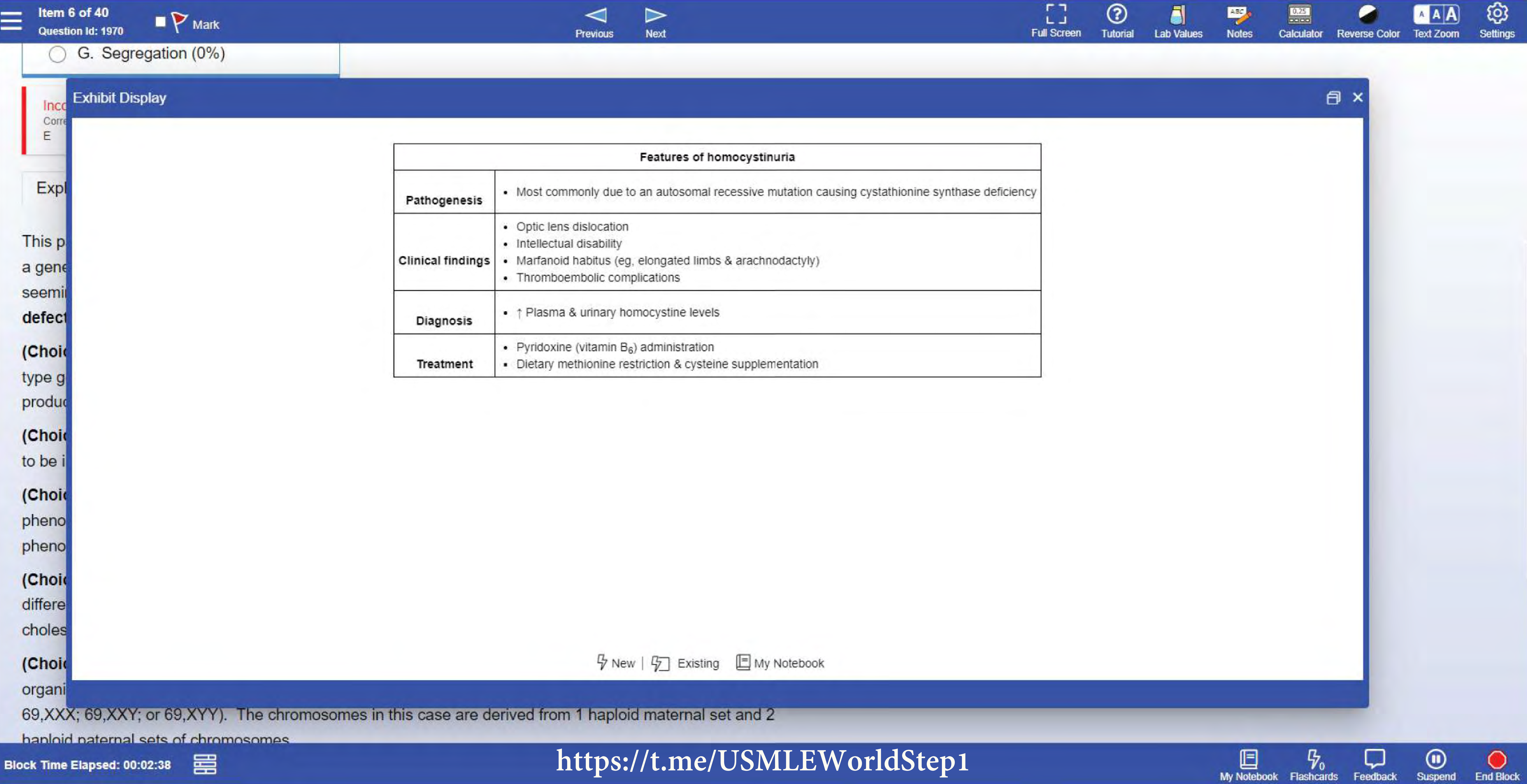
Item 6 of 40
Question Id: 1970
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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○ G. Segregation (0%)

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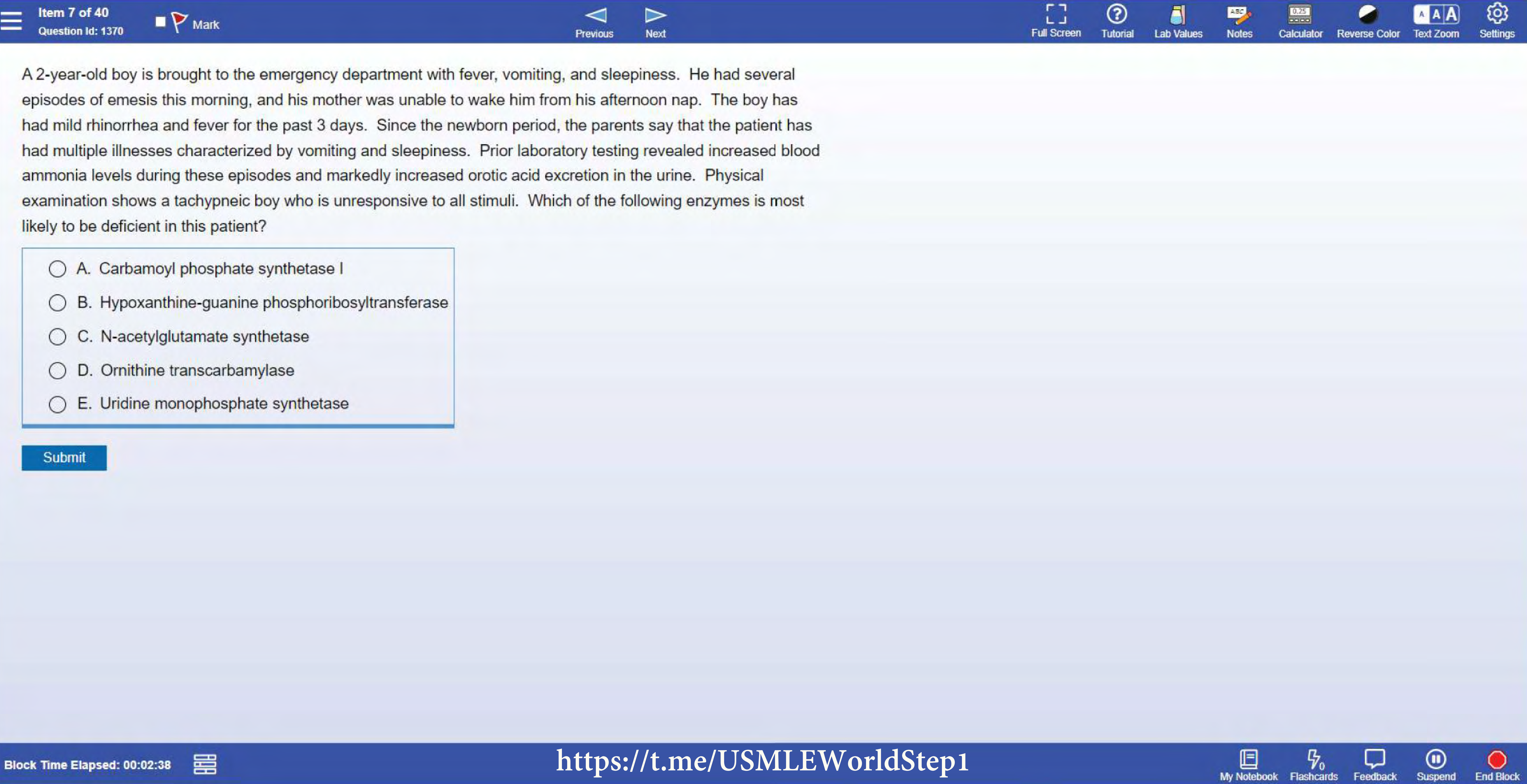
69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes

Features of homocystinuria	
Pathogenesis	- Most commonly due to an autosomal recessive mutation causing cystathionine synthase deficiency
Clinical findings	- Optic lens dislocation - Intellectual disability - Marfanoid habitus (eg, elongated limbs & arachnodactyly) - Thromboembolic complications
Diagnosis	- ↑ Plasma & urinary homocystine levels
Treatment	- Pyridoxine (vitamin B_6) administration - Dietary methionine restriction & cysteine supplementation


Item 7 of 40
Question Id: 1370
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:02:38
My Notebook
Flashcards
Feedback
Suspend
End Block

A 2-year-old boy is brought to the emergency department with fever, vomiting, and sleepiness. He had several episodes of emesis this morning, and his mother was unable to wake him from his afternoon nap. The boy has had mild rhinorrhea and fever for the past 3 days. Since the newborn period, the parents say that the patient has had multiple illnesses characterized by vomiting and sleepiness. Prior laboratory testing revealed increased blood ammonia levels during these episodes and markedly increased orotic acid excretion in the urine. Physical examination shows a tachypneic boy who is unresponsive to all stimuli. Which of the following enzymes is most likely to be deficient in this patient?

- ○ A. Carbamoyl phosphate synthetase I
- ○ B. Hypoxanthine-guanine phosphoribosyltransferase
- ○ C. N-acetylglutamate synthetase
- ○ D. Ornithine transcarbamylase
- ○ E. Uridine monophosphate synthetase

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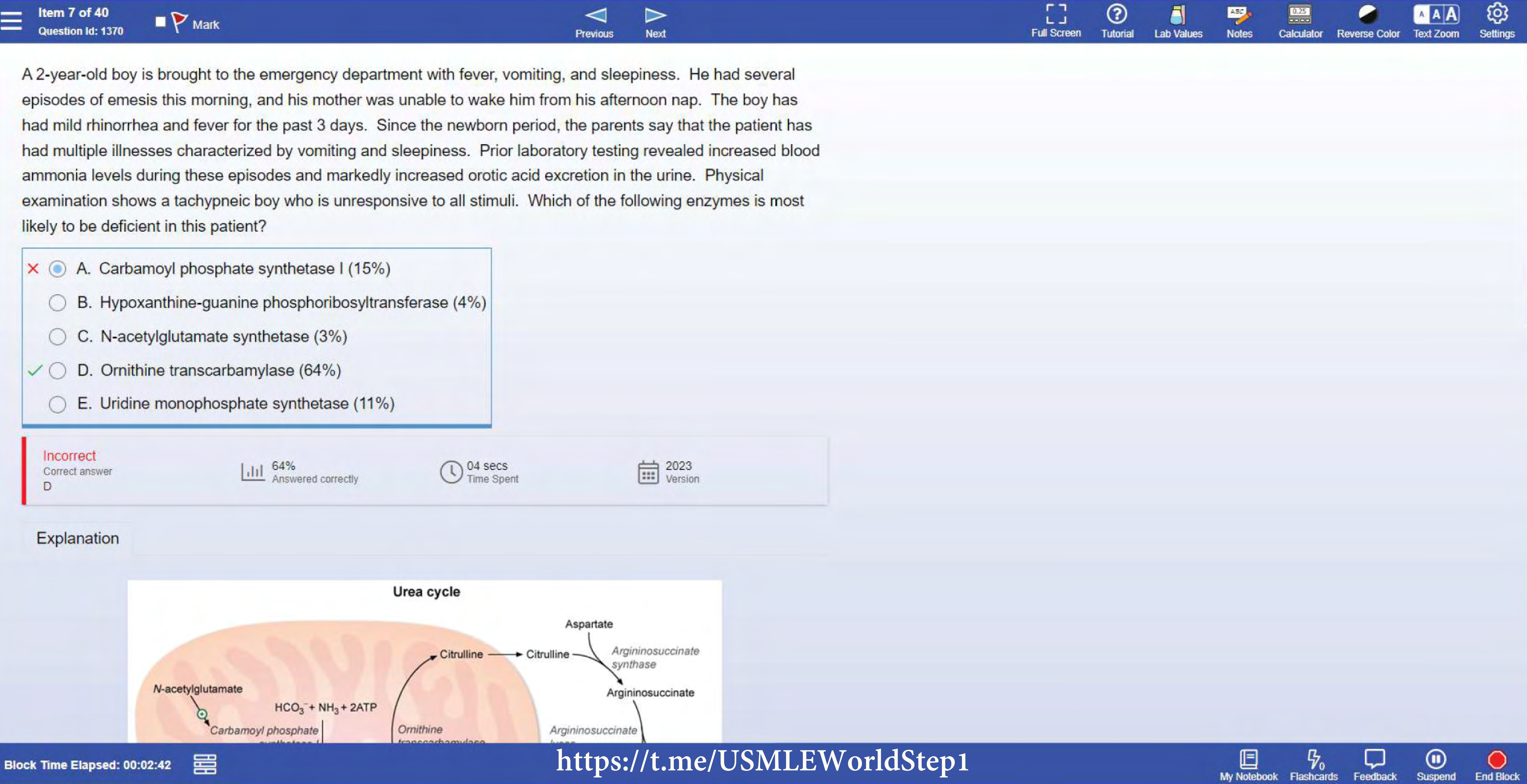
Item 7 of 40
Question Id: 1370
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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✗ ● A. Carbamoyl phosphate synthetase I (15%)

○ B. Hypoxanthine-guanine phosphoribosyltransferase (4%)

○ C. N-acetylglutamate synthetase (3%)

✓ ○ D. Ornithine transcarbamylase (64%)

○ E. Uridine monophosphate synthetase (11%)

Incorrect
Correct answer
D

64%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Urea cycle

Aspartate
Citrulline
Citrulline
Argininosuccinate synthase
Argininosuccinate
N-acetylglutamate
$HCO_3^- + NH_3 + 2ATP$
Carbamoyl phosphate
Ornithine
Argininosuccinate

Block Time Elapsed: 00:02:42
My Notebook
Flashcards
Feedback
Suspend
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Correct answer
D

Answered correctly

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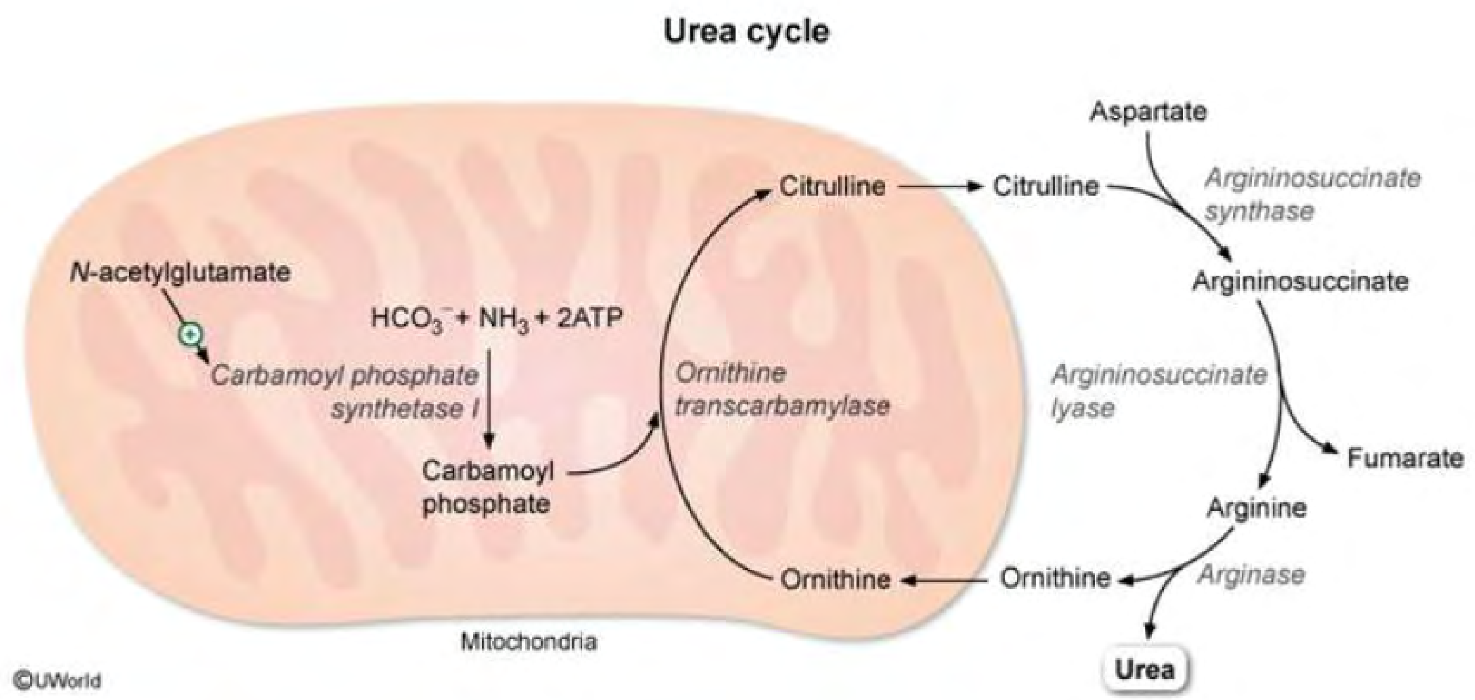
Exhibit Display

Urea cycle


Aspartate
Citrulline
Citrulline
Argininosuccinate synthase
N-acetylglutamate
$HCO_3^- + NH_3 + 2ATP$
Argininosuccinate
Carbamoyl phosphate synthetase I
Ornithine transcarbamylase
Argininosuccinate lyase
Fumarate
Carbamoyl phosphate
Arginine
Ornithine
Ornithine
Arginase
Urea
Mitochondria
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Patients also have **hyperammonemia** due to impaired ammonia excretion, which is a **metabolic emergency**.

Ornithine
Ornithine
Arginase
Mitochondria
Urea
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Ammonia generated from the metabolism of amino acids is converted into urea by the urea cycle. The combination of bicarbonate (HCO_3-), ammonia, and ATP is catalyzed by carbamoyl phosphate synthetase (rate-limiting enzyme in the urea cycle) to yield carbamoyl phosphate. Carbamoyl phosphate combines with ornithine to form citrulline in a reaction catalyzed by ornithine transcarbamylase. Citrulline enters the cytosol and is converted to argininosuccinate, which is then converted to arginine. The conversion of arginine to ornithine by arginase completes the urea cycle by releasing a urea molecule. N-acetylglutamate serves as a regulator of the urea cycle through activation of carbamoyl phosphate synthetase I.

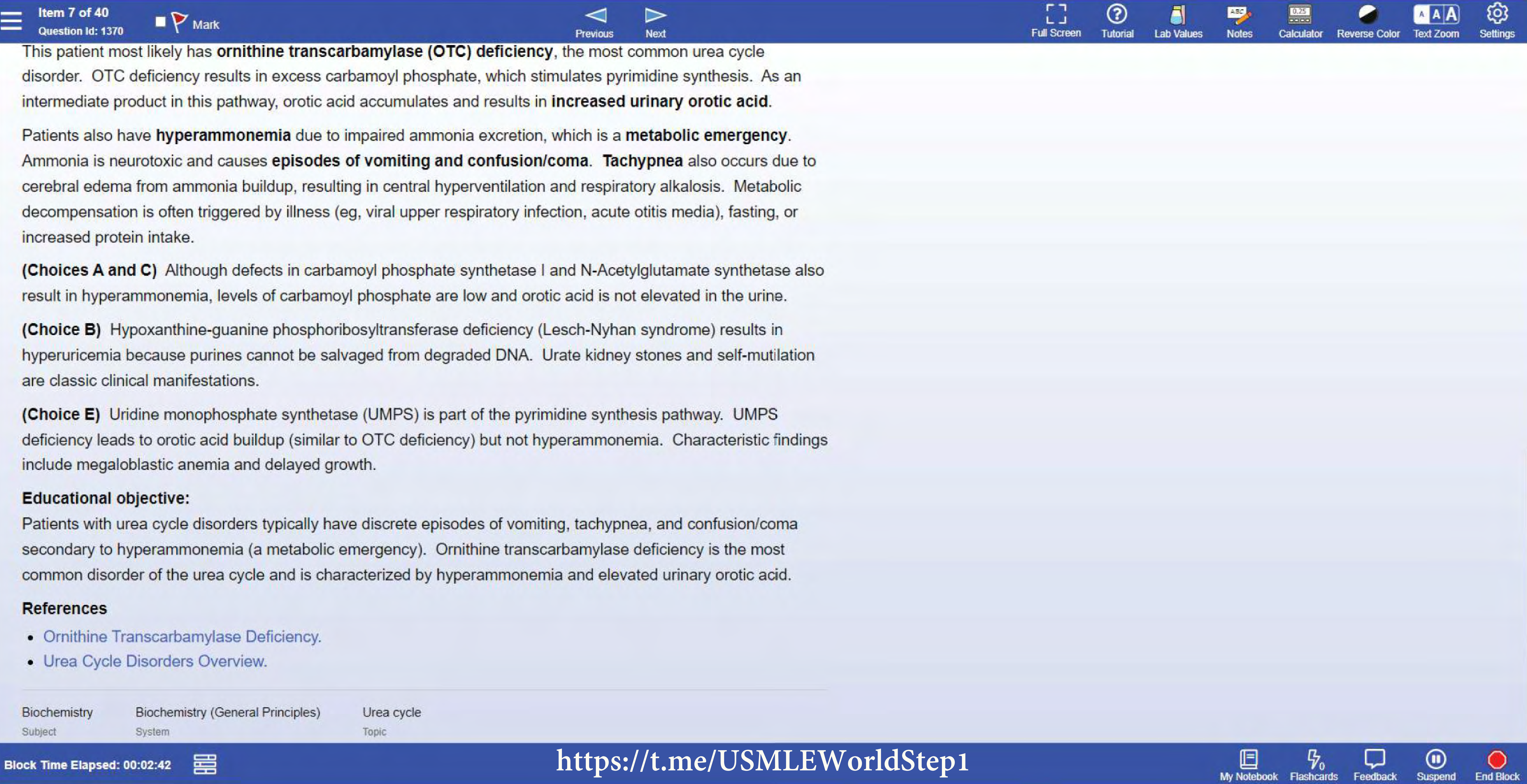
This patient most likely has **ornithine transcarbamylase (OTC) deficiency**, the most common urea cycle disorder. OTC deficiency results in excess carbamoyl phosphate, which stimulates pyrimidine synthesis. As an intermediate product in this pathway, orotic acid accumulates and results in **increased urinary orotic acid**.

Patients also have **hyperammonemia** due to impaired ammonia excretion, which is a **metabolic emergency**. Ammonia is neurotoxic and causes **episodes of vomiting and confusion/coma**. **Tachypnea** also occurs due to cerebral edema from ammonia buildup, resulting in central hyperventilation and respiratory alkalosis. Metabolic decompensation is often triggered by illness (eg, viral upper respiratory infection, acute otitis media), fasting, or increased protein intake.

(Choices A and C) Although defects in carbamoyl phosphate synthetase I and N-Acetylglutamate synthetase also result in hyperammonemia, levels of carbamoyl phosphate are low and orotic acid is not elevated in the urine.

(Choice B) Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) results in hyperuricemia because purines cannot be salvaged from degraded DNA. Urate kidney stones and self-mutilation are classic clinical manifestations.

(Choice E) Uridine monophosphate synthetase (UMPS) is part of the pyrimidine synthesis pathway. UMPS deficiency leads to orotic acid buildup (similar to OTC deficiency) but not hyperammonemia. Characteristic findings include megaloblastic anemia and delayed growth.



This patient most likely has **ornithine transcarbamylase (OTC) deficiency**, the most common urea cycle disorder. OTC deficiency results in excess carbamoyl phosphate, which stimulates pyrimidine synthesis. As an intermediate product in this pathway, orotic acid accumulates and results in **increased urinary orotic acid**.

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(Choice E) Uridine monophosphate synthetase (UMPS) is part of the pyrimidine synthesis pathway. UMPS deficiency leads to orotic acid buildup (similar to OTC deficiency) but not hyperammonemia. Characteristic findings include megaloblastic anemia and delayed growth.

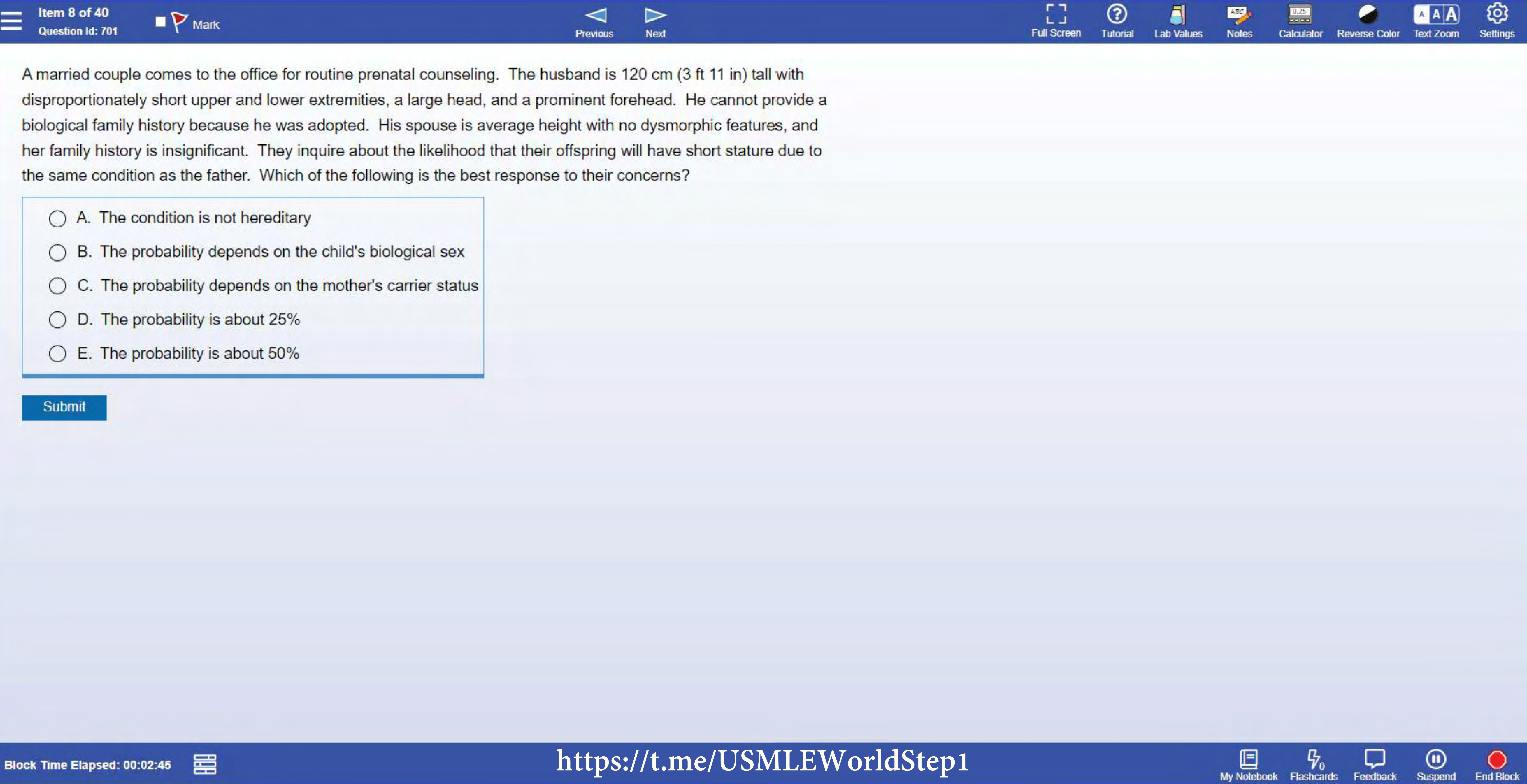
Educational objective:

Patients with urea cycle disorders typically have discrete episodes of vomiting, tachypnea, and confusion/coma secondary to hyperammonemia (a metabolic emergency). Ornithine transcarbamylase deficiency is the most common disorder of the urea cycle and is characterized by hyperammonemia and elevated urinary orotic acid.

References

- Ornithine Transcarbamylase Deficiency.
- Urea Cycle Disorders Overview.

Biochemistry	Biochemistry (General Principles)	Urea cycle
Subject	System	Topic


Item 8 of 40
Question Id: 701
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:02:45
My Notebook
Flashcards
Feedback
Suspend
End Block

A married couple comes to the office for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He cannot provide a biological family history because he was adopted. His spouse is average height with no dysmorphic features, and her family history is insignificant. They inquire about the likelihood that their offspring will have short stature due to the same condition as the father. Which of the following is the best response to their concerns?

○ A. The condition is not hereditary

○ B. The probability depends on the child's biological sex

○ C. The probability depends on the mother's carrier status

○ D. The probability is about 25%

○ E. The probability is about 50%

A married couple comes to the office for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He cannot provide a biological family history because he was adopted. His spouse is average height with no dysmorphic features, and her family history is insignificant. They inquire about the likelihood that their offspring will have short stature due to the same condition as the father. Which of the following is the best response to their concerns?

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- ○ C. The probability depends on the mother's carrier status
- ○ D. The probability is about 25%
- ✓ ○ E. The probability is about 50%

Incorrect
Correct answer
E

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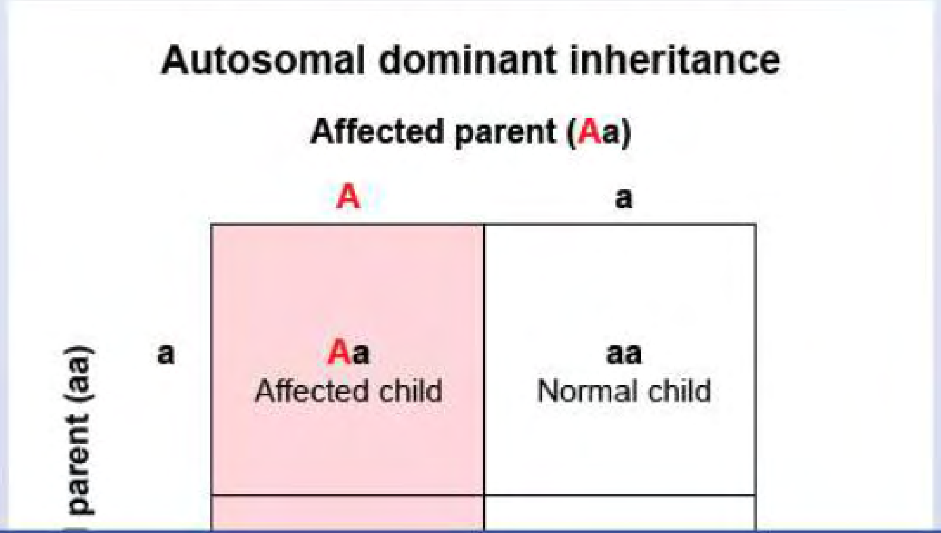
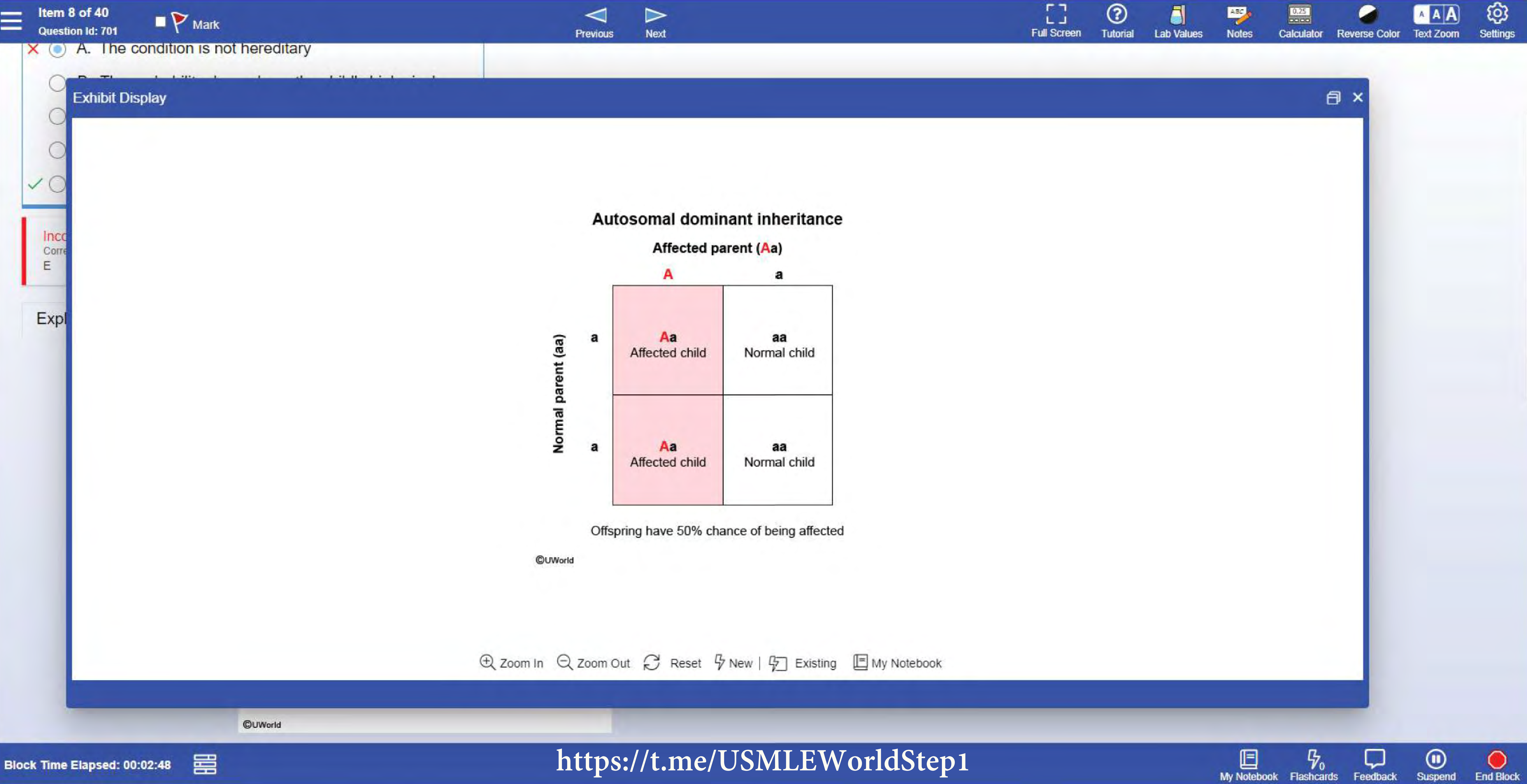
Explanation





Item 8 of 40
Question Id: 701
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

☒ ● A. The condition is not hereditary

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Exhibit Display

Autosomal dominant inheritance

Affected parent (Aa)

Normal parent (aa)	A	a
a	**Aa** Affected child	**aa** Normal child
a	**Aa** Affected child	**aa** Normal child

Offspring have 50% chance of being affected

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Zoom Out
Reset
New
Existing
My Notebook

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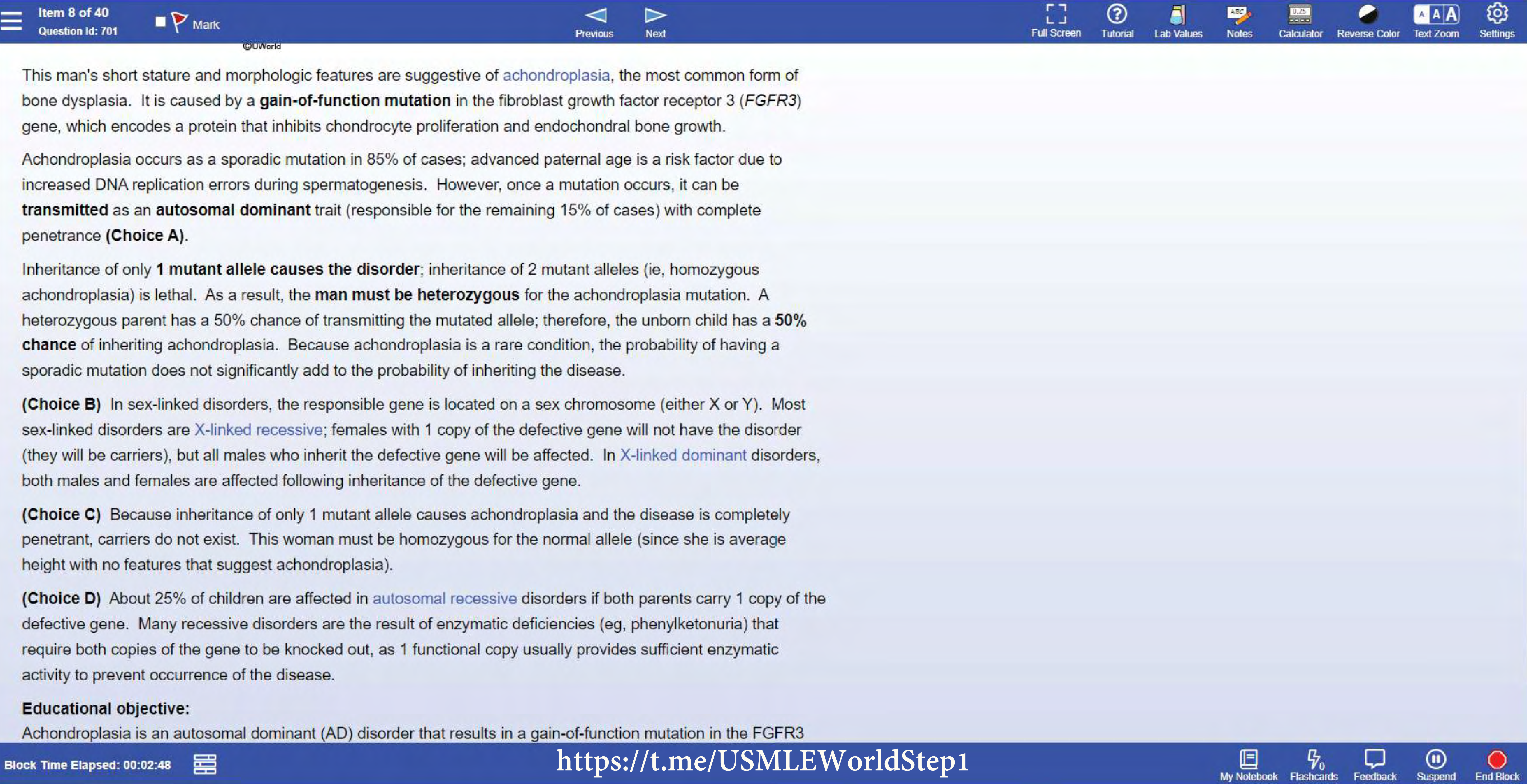
Block Time Elapsed: 00:02:48
My Notebook
Flashcards
Feedback
Suspend
End Block



Item 8 of 40
Question Id: 701

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This man's short stature and morphologic features are suggestive of achondroplasia, the most common form of bone dysplasia. It is caused by a **gain-of-function mutation** in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which encodes a protein that inhibits chondrocyte proliferation and endochondral bone growth.

Achondroplasia occurs as a sporadic mutation in 85% of cases; advanced paternal age is a risk factor due to increased DNA replication errors during spermatogenesis. However, once a mutation occurs, it can be **transmitted** as an **autosomal dominant** trait (responsible for the remaining 15% of cases) with complete penetrance **(Choice A)**.

Inheritance of only **1 mutant allele causes the disorder**; inheritance of 2 mutant alleles (ie, homozygous achondroplasia) is lethal. As a result, the **man must be heterozygous** for the achondroplasia mutation. A heterozygous parent has a 50% chance of transmitting the mutated allele; therefore, the unborn child has a **50% chance** of inheriting achondroplasia. Because achondroplasia is a rare condition, the probability of having a sporadic mutation does not significantly add to the probability of inheriting the disease.

(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y). Most sex-linked disorders are X-linked recessive; females with 1 copy of the defective gene will not have the disorder (they will be carriers), but all males who inherit the defective gene will be affected. In X-linked dominant disorders, both males and females are affected following inheritance of the defective gene.

(Choice C) Because inheritance of only 1 mutant allele causes achondroplasia and the disease is completely penetrant, carriers do not exist. This woman must be homozygous for the normal allele (since she is average height with no features that suggest achondroplasia).

(Choice D) About 25% of children are affected in autosomal recessive disorders if both parents carry 1 copy of the defective gene. Many recessive disorders are the result of enzymatic deficiencies (eg, phenylketonuria) that require both copies of the gene to be knocked out, as 1 functional copy usually provides sufficient enzymatic activity to prevent occurrence of the disease.

Educational objective:

Achondroplasia is an autosomal dominant (AD) disorder that results in a gain-of-function mutation in the FGFR3

Block Time Elapsed: 00:02:48

Item 8 of 40
Question Id: 701
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Educational objective:
Achondroplasia is an autosomal dominant (AD) disorder that results in a gain-of-function mutation in the FGFR3 gene. Most individuals affected by AD disorders are heterozygous and have a 50% chance of transmitting the mutation to their offspring.

Genetics	Genetics (General Principles)	Achondroplasia
Subject	System	Topic

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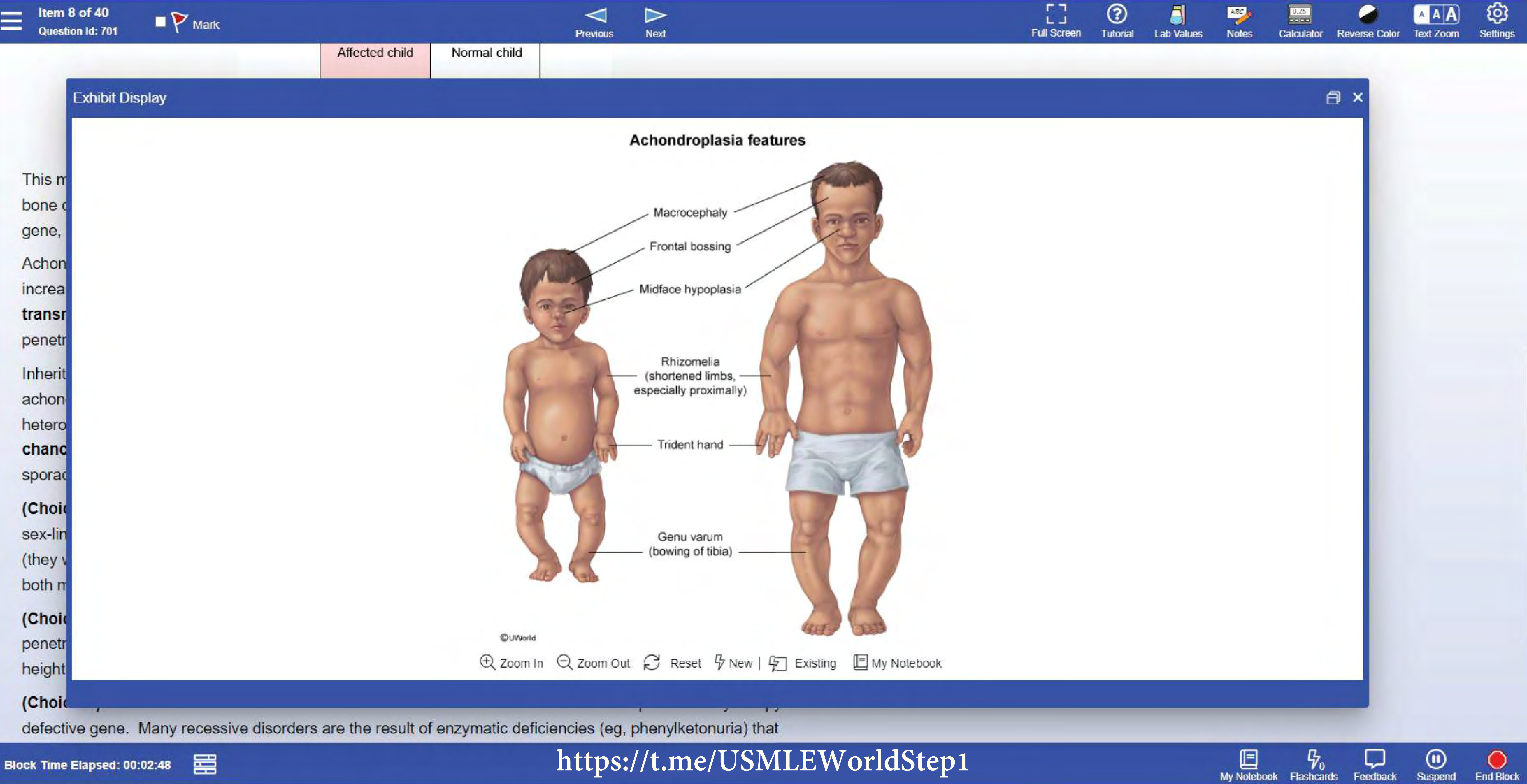
Item 8 of 40
Question Id: 701
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Affected child
Normal child
Exhibit Display
Macrocephaly
Frontal bossing
Midface hypoplasia
Rhizomelia (shortened limbs, especially proximally)
Trident hand
Genu varum (bowing of tibia)
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Zoom Out
Reset
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My Notebook
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My Notebook
Flashcards
Feedback
Suspend
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Achondroplasia features

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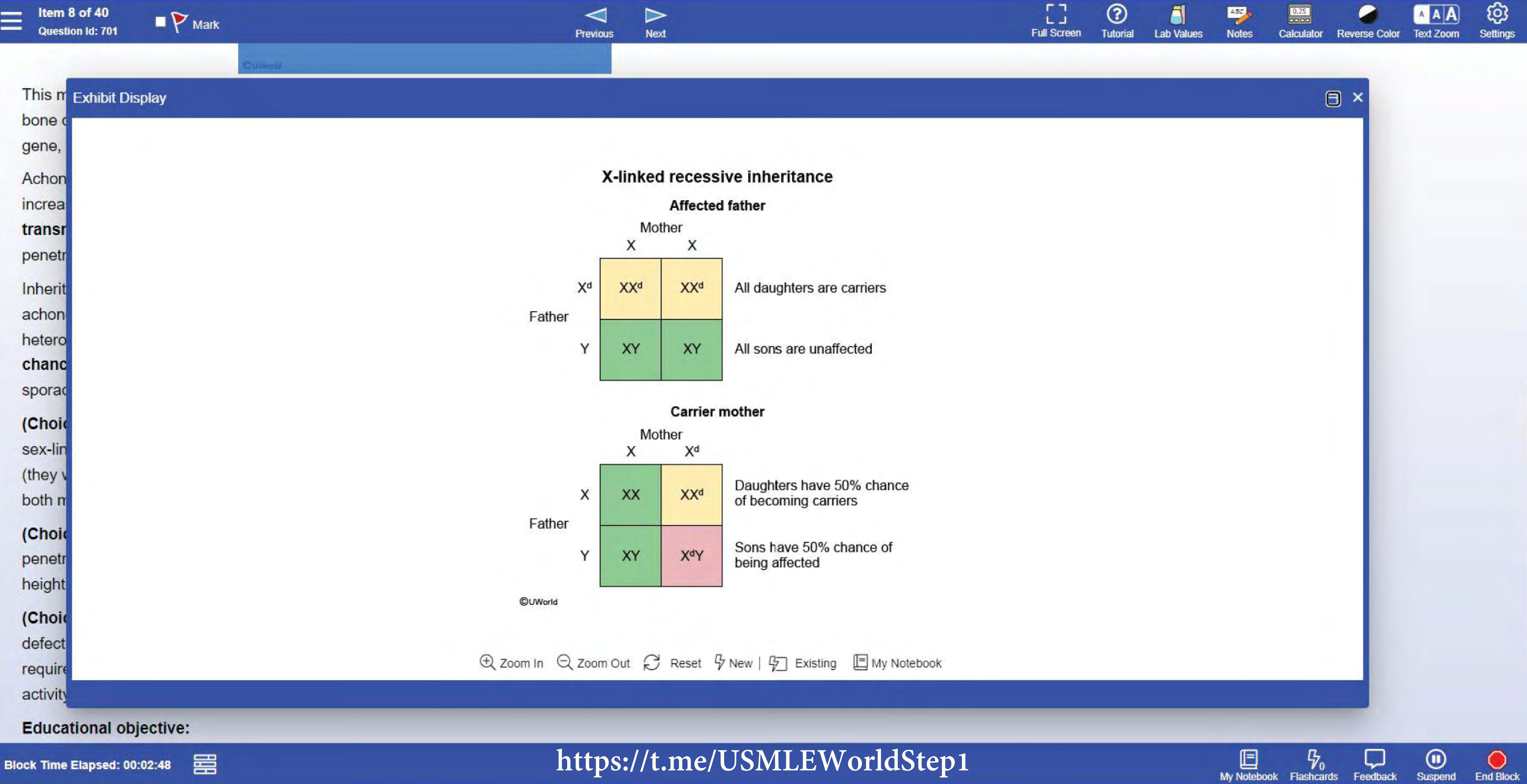
Item 8 of 40
Question Id: 701
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Zoom In
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Block Time Elapsed: 00:02:48
My Notebook
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Educational objective:

X-linked recessive inheritance

Affected father

Father \ Mother	X	X	
X^d	XX^d	XX^d	All daughters are carriers
Y	XY	XY	All sons are unaffected

Carrier mother

Father \ Mother	X	X^d	
X	XX	XX^d	Daughters have 50% chance of becoming carriers
Y	XY	X^dY	Sons have 50% chance of being affected

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Item 8 of 40
Question Id: 701

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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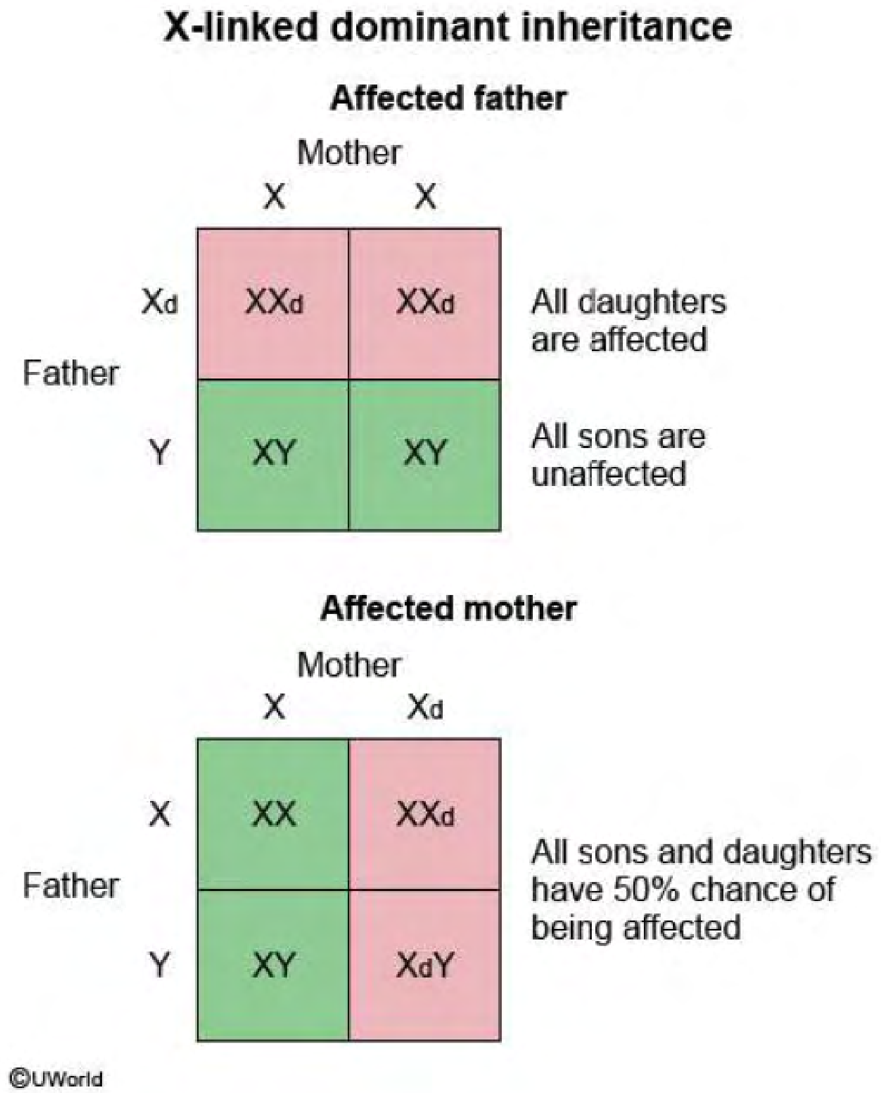

X-linked dominant inheritance

Affected father

		Mother X	Mother X
Father	X_d	XX_d	XX_d
Father	Y	XY	XY

All daughters are affected

All sons are unaffected

Affected mother

		Mother X	Mother X_d
Father	X	XX	XX_d
Father	Y	XY	X_dY

All sons and daughters have 50% chance of being affected

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transmitted as an **autosomal dominant** trait (responsible for the remaining 15% of cases) with complete

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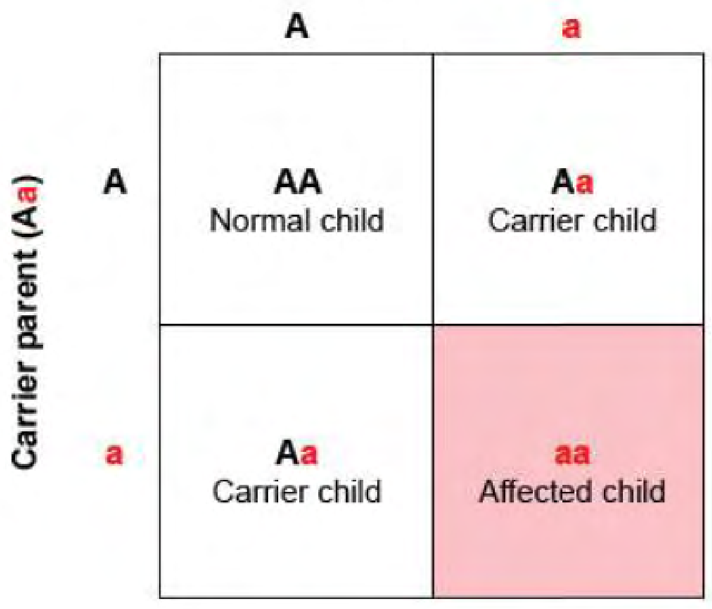
Autosomal recessive inheritance

Carrier parent (Aa)



	A	a
A	**AA** Normal child	**Aa** Carrier child
a	**Aa** Carrier child	**aa** Affected child

Offspring have 25% chance of being affected

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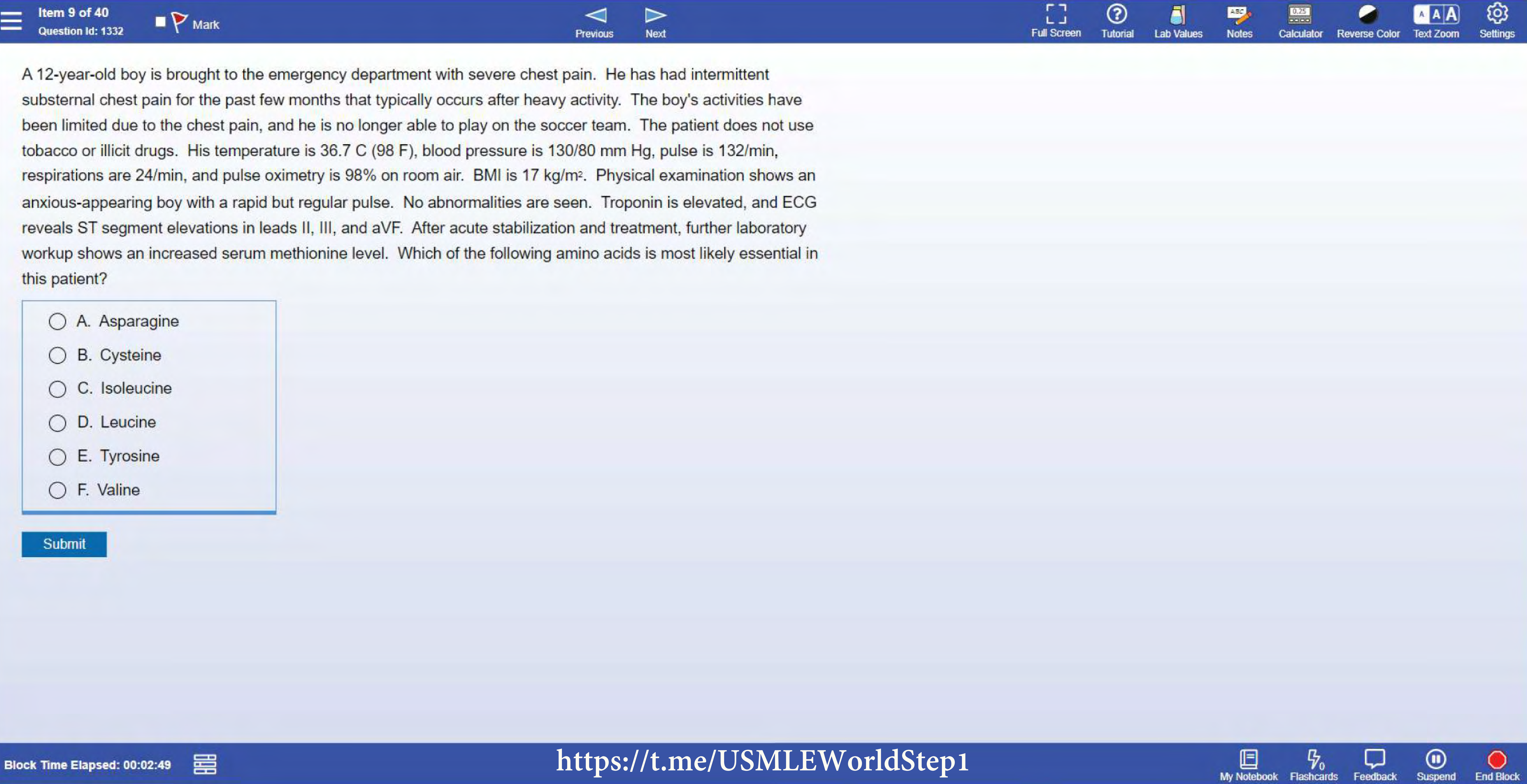
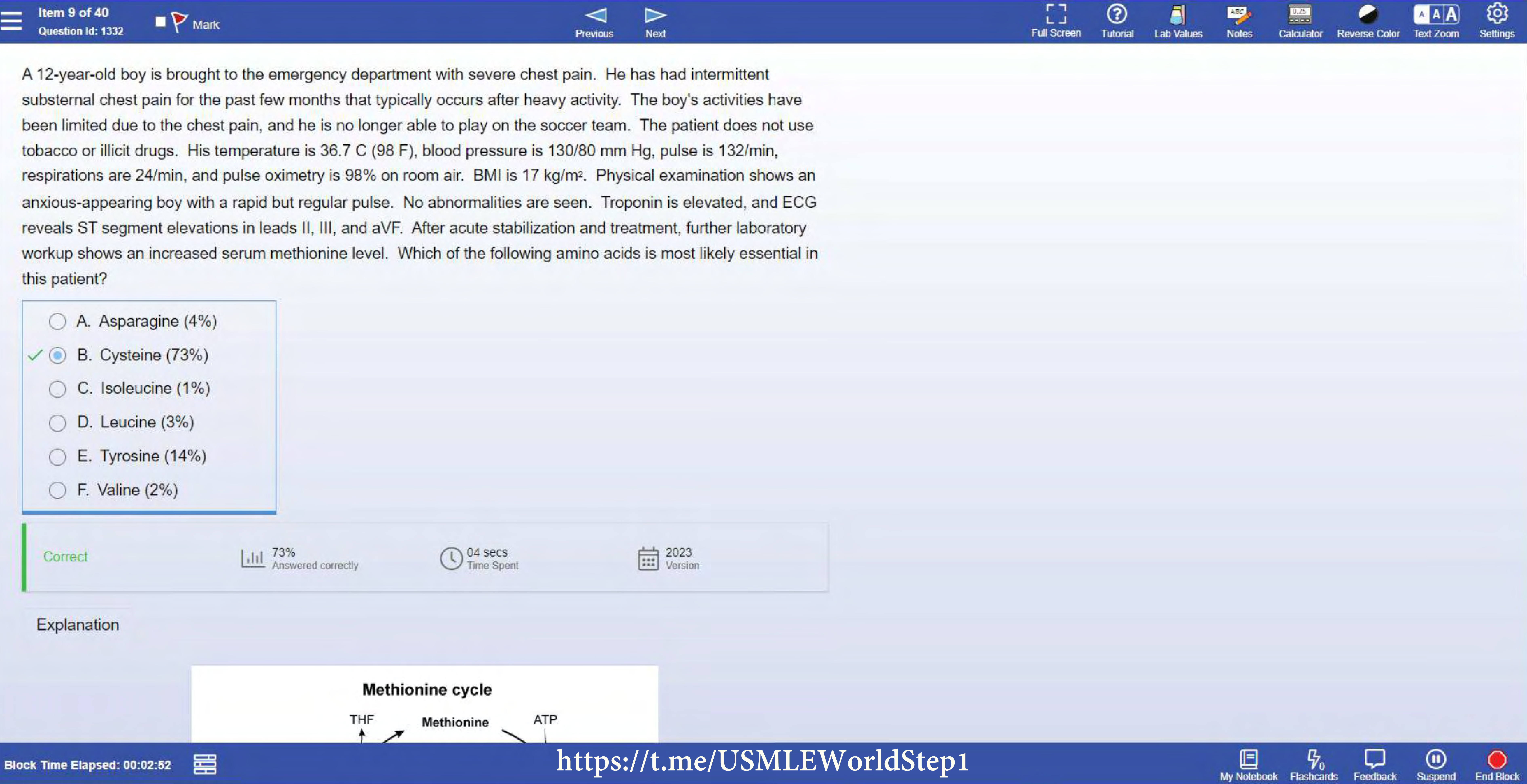

Item 9 of 40
Question Id: 1332
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:02:49
My Notebook
Flashcards
Feedback
Suspend
End Block

A 12-year-old boy is brought to the emergency department with severe chest pain. He has had intermittent substernal chest pain for the past few months that typically occurs after heavy activity. The boy's activities have been limited due to the chest pain, and he is no longer able to play on the soccer team. The patient does not use tobacco or illicit drugs. His temperature is 36.7 C (98 F), blood pressure is 130/80 mm Hg, pulse is 132/min, respirations are 24/min, and pulse oximetry is 98% on room air. BMI is 17 kg/m^2. Physical examination shows an anxious-appearing boy with a rapid but regular pulse. No abnormalities are seen. Troponin is elevated, and ECG reveals ST segment elevations in leads II, III, and aVF. After acute stabilization and treatment, further laboratory workup shows an increased serum methionine level. Which of the following amino acids is most likely essential in this patient?

- ○ A. Asparagine
- ○ B. Cysteine
- ○ C. Isoleucine
- ○ D. Leucine
- ○ E. Tyrosine
- ○ F. Valine



Item 9 of 40
Question Id: 1332
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ A. Asparagine (4%)
- ✓ ● B. Cysteine (73%)
- ○ C. Isoleucine (1%)
- ○ D. Leucine (3%)
- ○ E. Tyrosine (14%)
- ○ F. Valine (2%)

Correct

73% Answered correctly

04 secs Time Spent

2023 Version

Explanation

Methionine cycle

THF
Methionine
ATP

Block Time Elapsed: 00:02:52

My Notebook
Flashcards
Feedback
Suspend
End Block

Item 9 of 40
Question Id: 1332

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Correct

73% Answered correctly

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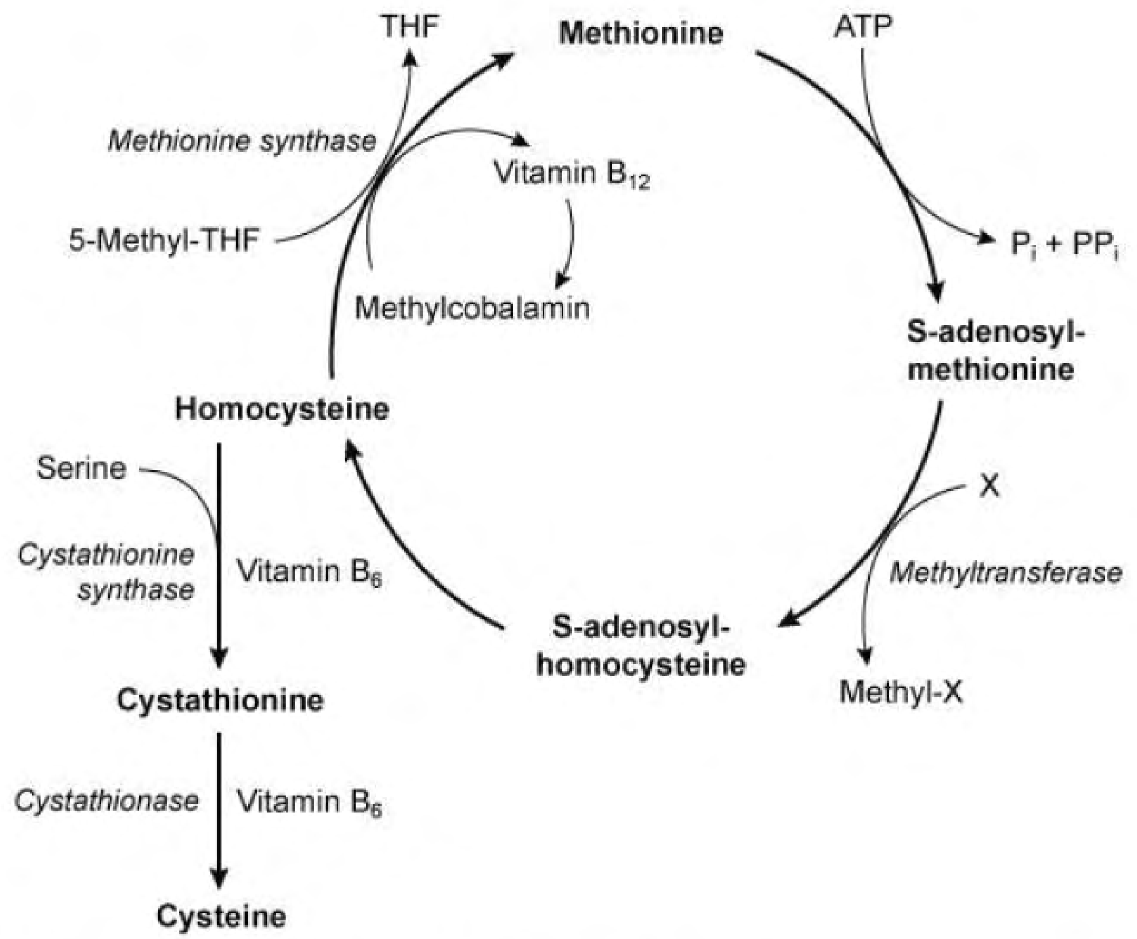
2023 Version

Expl

Exhibit Display

Methionine cycle


THF
Methionine
ATP
Methionine synthase
Vitamin B_{12}
5-Methyl-THF
P_i + PP_i
Methylcobalamin
S-adenosyl-methionine
Homocysteine
Serine
X
Cystathionine synthase
Vitamin B_6
Methyltransferase
S-adenosyl-homocysteine
Methyl-X
Cystathionine
Cystathionase
Vitamin B_6
Cysteine

P_i = inorganic phosphate; **PP_i** = inorganic pyrophosphate (diphosphate);
THF = tetrahydrofolate.

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homocysteine to cystathionine requires the enzyme cystathionine synthase, the amino acid serine, and the

cofactor vitamin B. Cystathionine is then converted to cysteine by the enzyme cystathionase, which also requires

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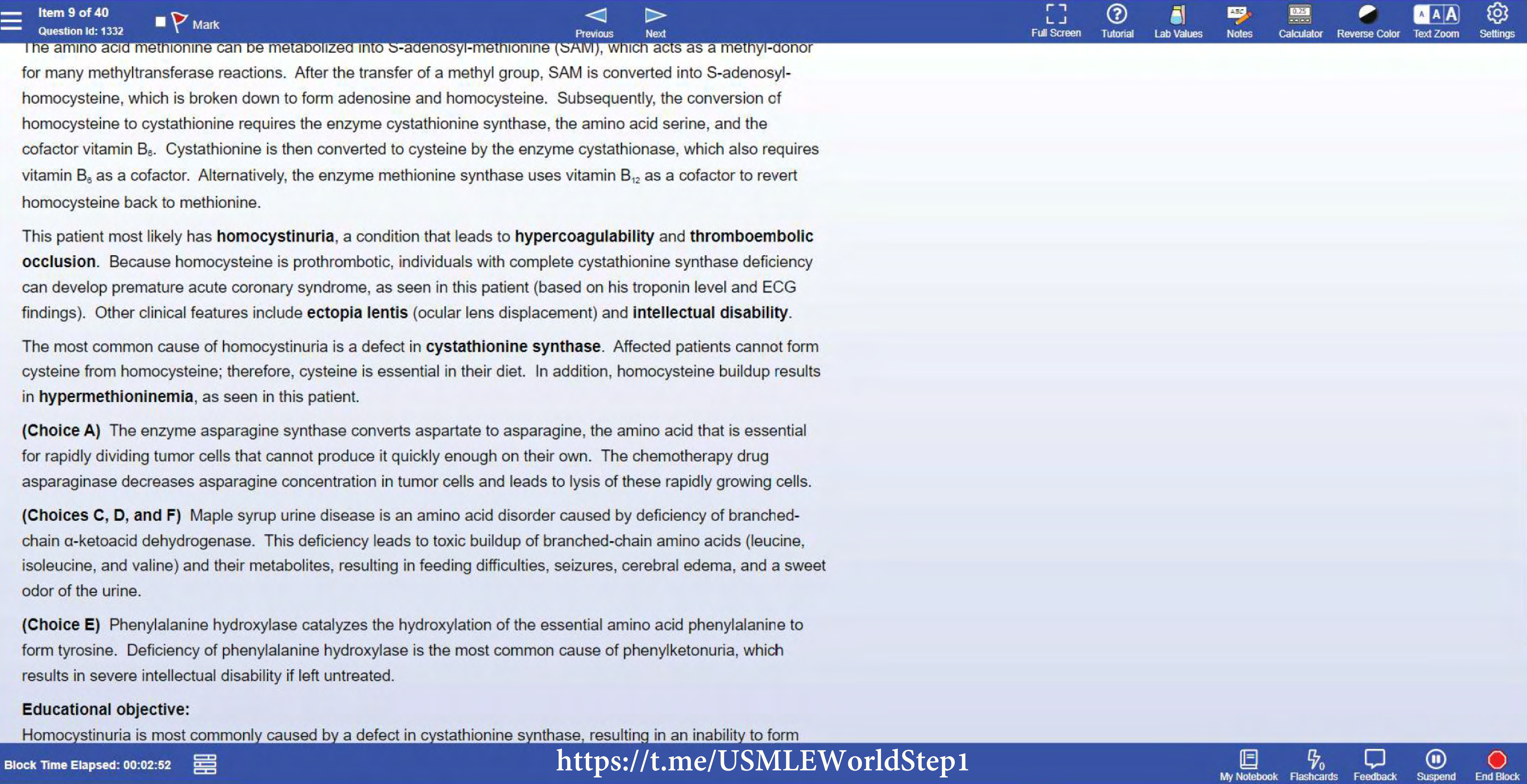
My Notebook Flashcards Feedback Suspend End Block



The amino acid methionine can be metabolized into S-adenosyl-methionine (SAM), which acts as a methyl-donor for many methyltransferase reactions. After the transfer of a methyl group, SAM is converted into S-adenosyl-homocysteine, which is broken down to form adenosine and homocysteine. Subsequently, the conversion of homocysteine to cystathionine requires the enzyme cystathionine synthase, the amino acid serine, and the cofactor vitamin B_6. Cystathionine is then converted to cysteine by the enzyme cystathionase, which also requires vitamin B_6 as a cofactor. Alternatively, the enzyme methionine synthase uses vitamin B_{12} as a cofactor to revert homocysteine back to methionine.

This patient most likely has **homocystinuria**, a condition that leads to **hypercoagulability** and **thromboembolic occlusion**. Because homocysteine is prothrombotic, individuals with complete cystathionine synthase deficiency can develop premature acute coronary syndrome, as seen in this patient (based on his troponin level and ECG findings). Other clinical features include **ectopia lentis** (ocular lens displacement) and **intellectual disability**.

The most common cause of homocystinuria is a defect in **cystathionine synthase**. Affected patients cannot form cysteine from homocysteine; therefore, cysteine is essential in their diet. In addition, homocysteine buildup results in **hypermethioninemia**, as seen in this patient.

(Choice A) The enzyme asparagine synthase converts aspartate to asparagine, the amino acid that is essential for rapidly dividing tumor cells that cannot produce it quickly enough on their own. The chemotherapy drug asparaginase decreases asparagine concentration in tumor cells and leads to lysis of these rapidly growing cells.

(Choices C, D, and F) Maple syrup urine disease is an amino acid disorder caused by deficiency of branched-chain α-ketoacid dehydrogenase. This deficiency leads to toxic buildup of branched-chain amino acids (leucine, isoleucine, and valine) and their metabolites, resulting in feeding difficulties, seizures, cerebral edema, and a sweet odor of the urine.

(Choice E) Phenylalanine hydroxylase catalyzes the hydroxylation of the essential amino acid phenylalanine to form tyrosine. Deficiency of phenylalanine hydroxylase is the most common cause of phenylketonuria, which results in severe intellectual disability if left untreated.

Educational objective:

Homocystinuria is most commonly caused by a defect in cystathionine synthase, resulting in an inability to form

Item 9 of 40
Question Id: 1332
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

findings). Other clinical features include **ectopia lentis** (ocular lens displacement) and **intellectual disability**.

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(Choice E) Phenylalanine hydroxylase catalyzes the hydroxylation of the essential amino acid phenylalanine to form tyrosine. Deficiency of phenylalanine hydroxylase is the most common cause of phenylketonuria, which results in severe intellectual disability if left untreated.

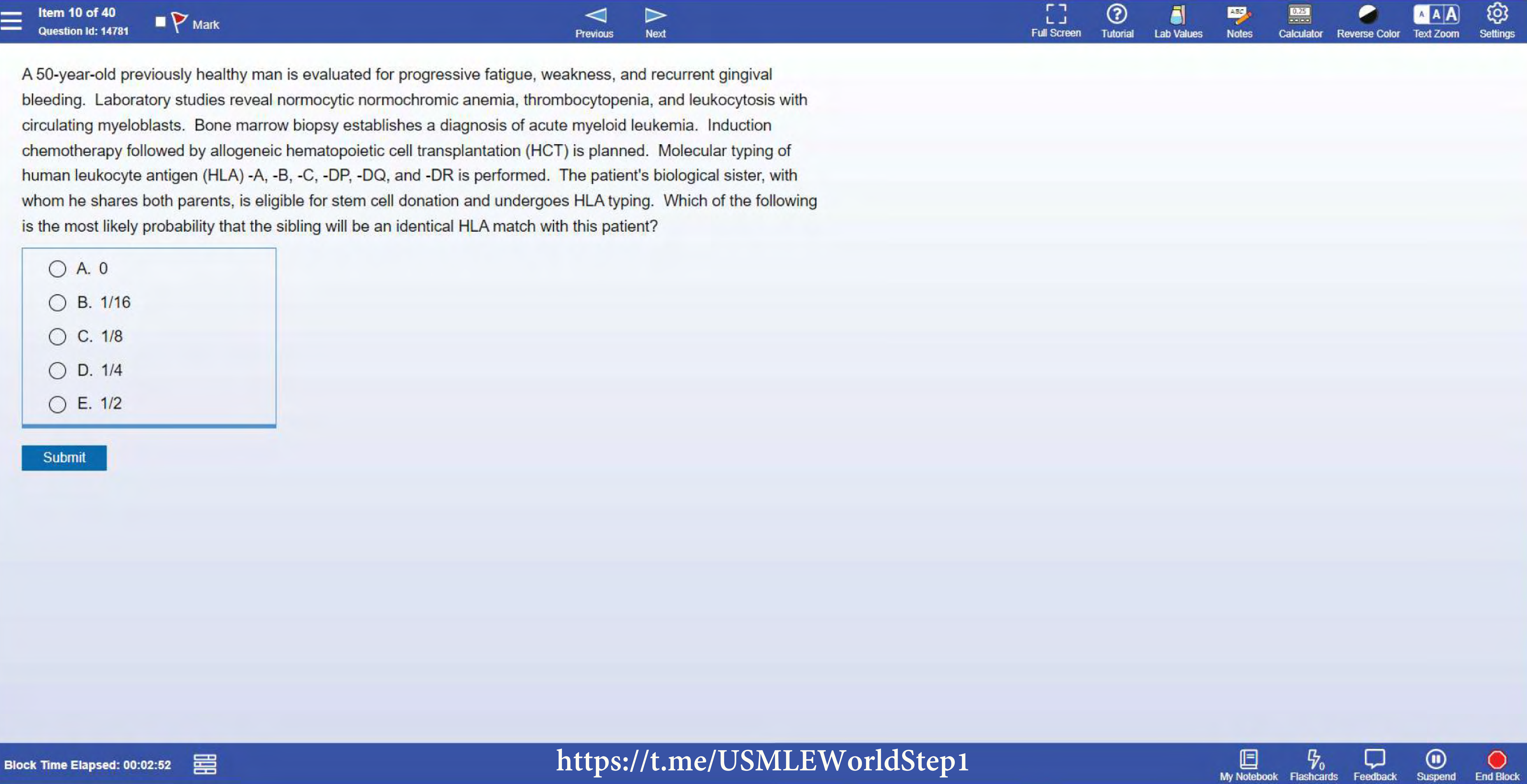
Educational objective:

Homocystinuria is most commonly caused by a defect in cystathionine synthase, resulting in an inability to form cysteine from homocysteine. Cysteine becomes essential in affected patients, and homocysteine buildup leads to elevated methionine. Homocysteine is prothrombotic, resulting in premature thromboembolic events (eg, atherosclerosis, acute coronary syndrome) in these patients.

References

- Hypermethioninemias of genetic and non-genetic origin: A review.
- Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects.

Biochemistry	Biochemistry (General Principles)	Homocysteine
Subject	System	Topic


Item 10 of 40
Question Id: 14781
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 50-year-old previously healthy man is evaluated for progressive fatigue, weakness, and recurrent gingival bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical HLA match with this patient?

○ A. 0
○ B. 1/16
○ C. 1/8
○ D. 1/4
○ E. 1/2

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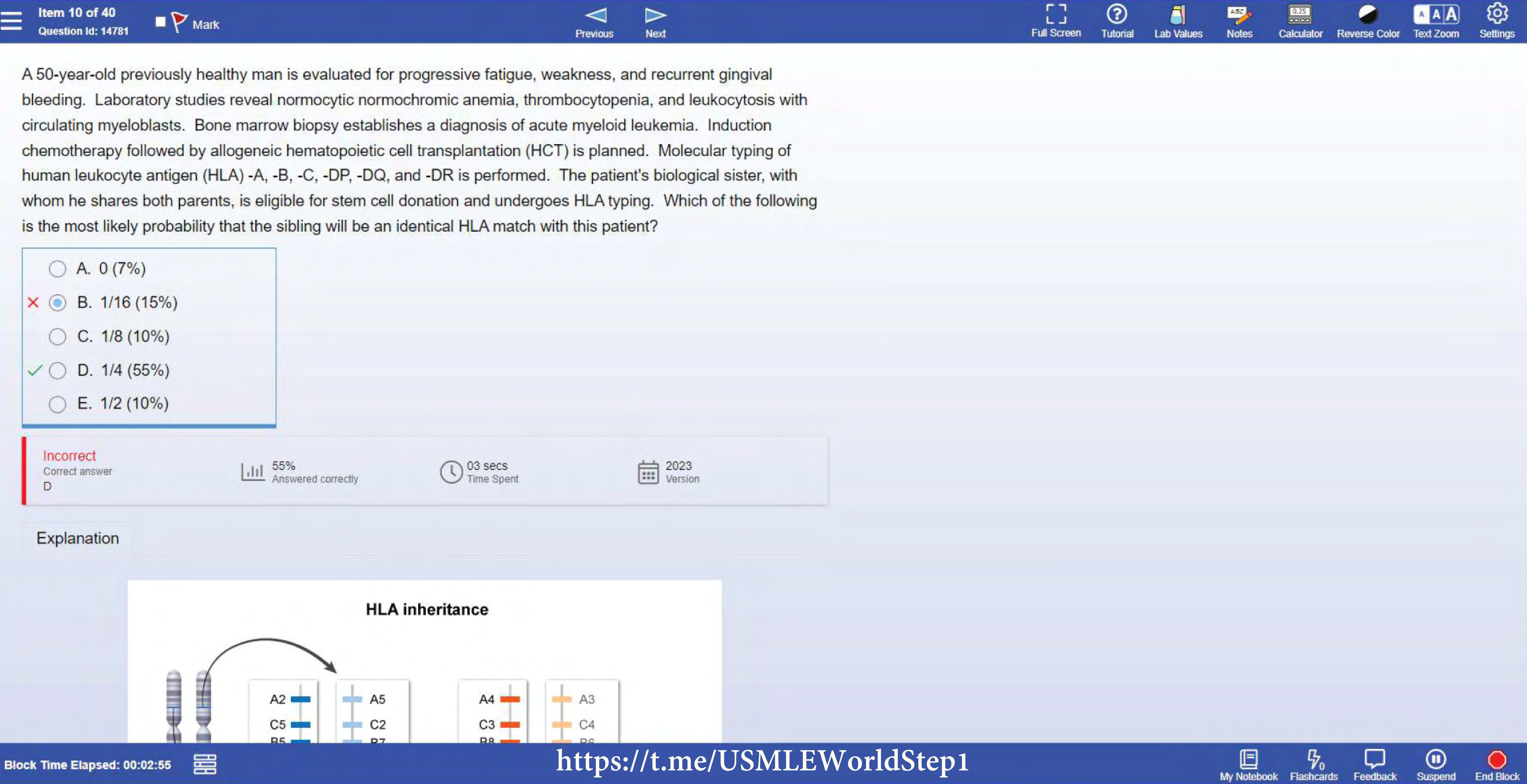
Item 10 of 40
Question Id: 14781
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
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○ A. 0 (7%)

✗ ● B. 1/16 (15%)

○ C. 1/8 (10%)

✓ ○ D. 1/4 (55%)

○ E. 1/2 (10%)

Incorrect
Correct answer
D

55%
Answered correctly

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Explanation

HLA inheritance

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C5
A5
C2
A4
C3
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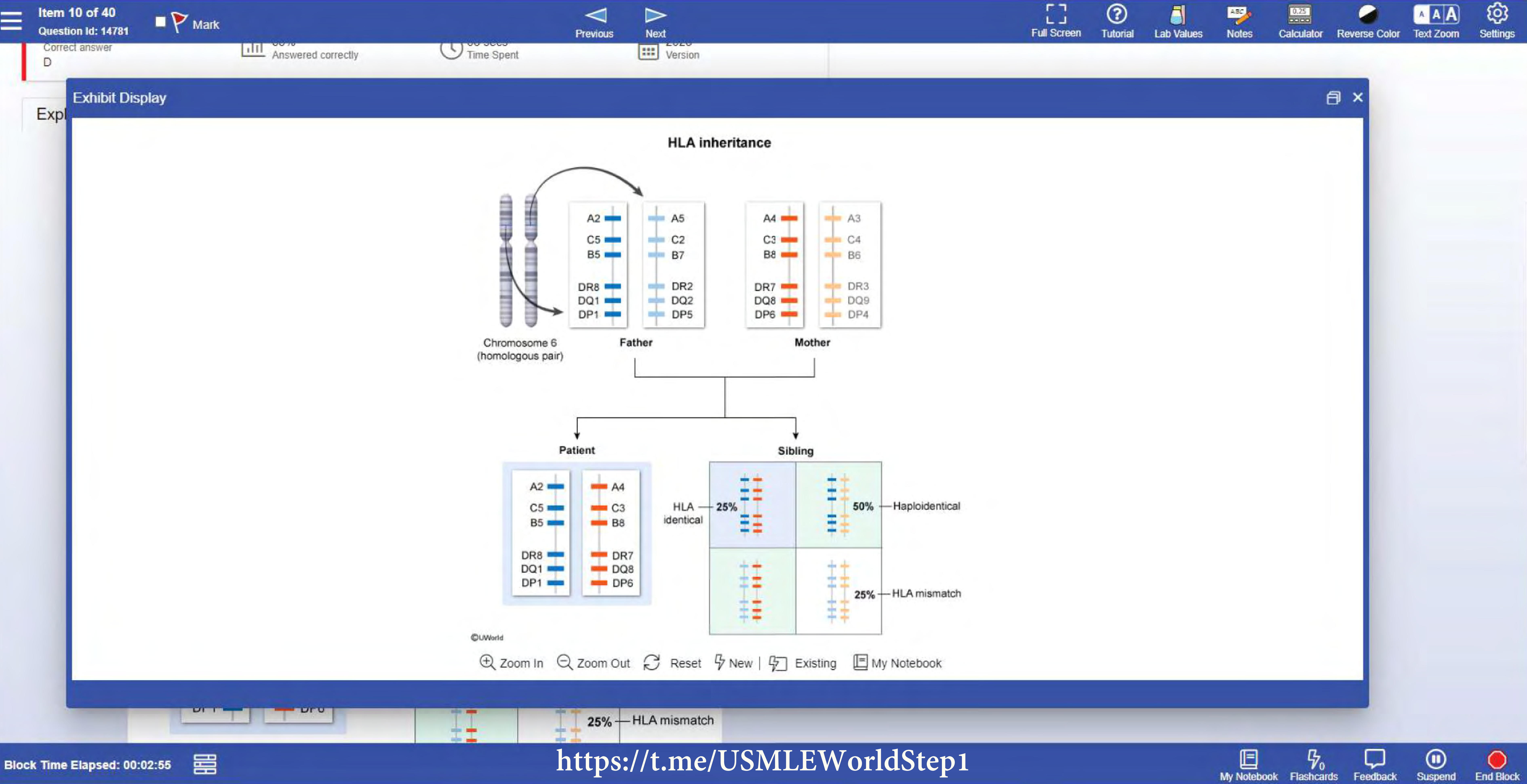Item 10 of 40
Question Id: 14781
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Correct answer
D
Answered correctly
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Version
Expl
Exhibit Display
HLA inheritance
A2
C5
B5
DR8
DQ1
DP1
A5
C2
B7
DR2
DQ2
DP5
A4
C3
B8
DR7
DQ8
DP6
A3
C4
B6
DR3
DQ9
DP4
Chromosome 6
(homologous pair)
Father
Mother
Patient
Sibling
A2
C5
B5
DR8
DQ1
DP1
A4
C3
B8
DR7
DQ8
DP6
HLA identical
25%
50%
Haploidentical
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HLA mismatch
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HLA mismatch
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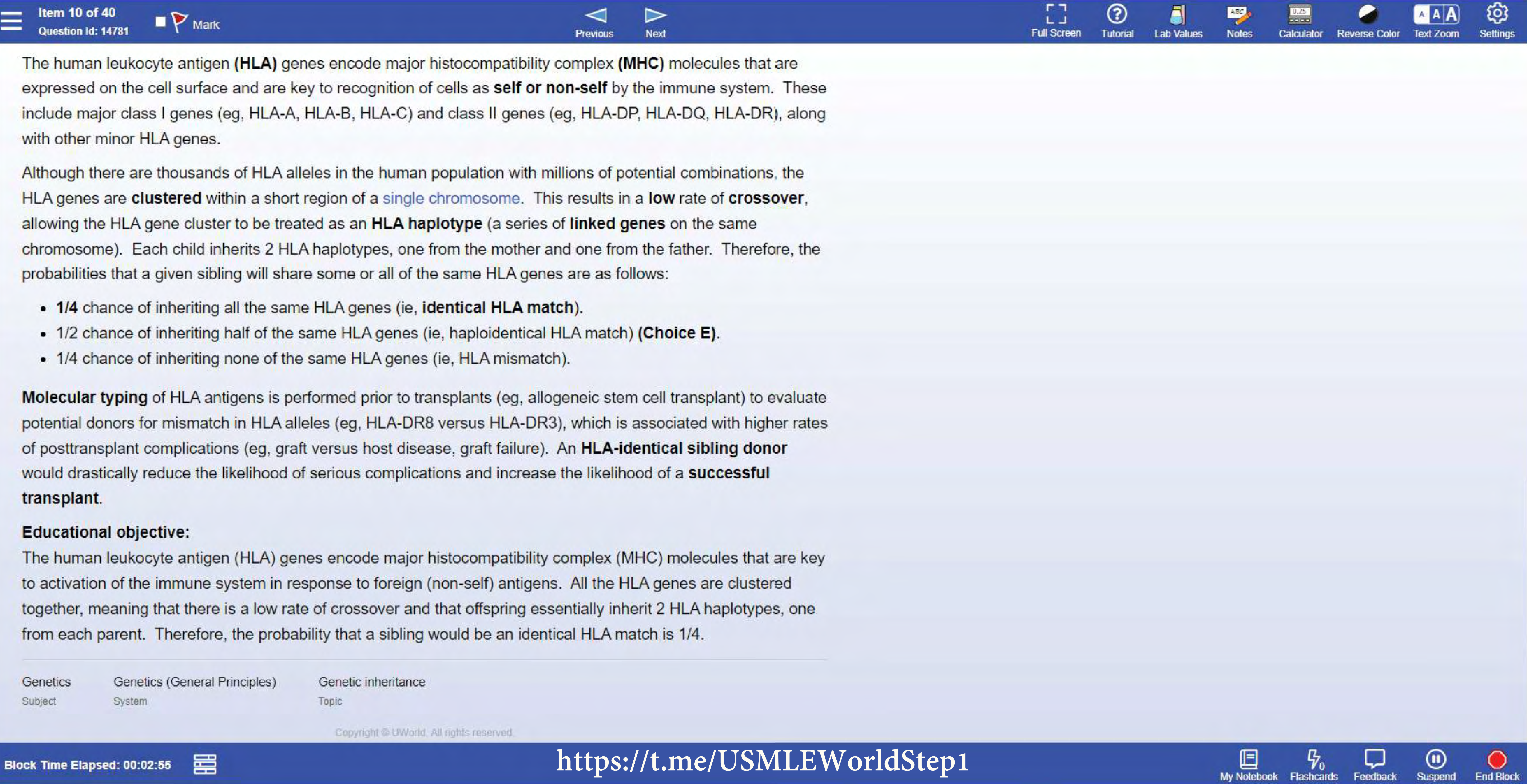

The human leukocyte antigen **(HLA)** genes encode major histocompatibility complex **(MHC)** molecules that are expressed on the cell surface and are key to recognition of cells as **self or non-self** by the immune system. These include major class I genes (eg, HLA-A, HLA-B, HLA-C) and class II genes (eg, HLA-DP, HLA-DQ, HLA-DR), along with other minor HLA genes.

Although there are thousands of HLA alleles in the human population with millions of potential combinations, the HLA genes are **clustered** within a short region of a single chromosome. This results in a **low** rate of **crossover**, allowing the HLA gene cluster to be treated as an **HLA haplotype** (a series of **linked genes** on the same chromosome). Each child inherits 2 HLA haplotypes, one from the mother and one from the father. Therefore, the probabilities that a given sibling will share some or all of the same HLA genes are as follows:

- **1/4** chance of inheriting all the same HLA genes (ie, **identical HLA match**).
- 1/2 chance of inheriting half of the same HLA genes (ie, haploidentical HLA match) **(Choice E)**.
- 1/4 chance of inheriting none of the same HLA genes (ie, HLA mismatch).

Molecular typing of HLA antigens is performed prior to transplants (eg, allogeneic stem cell transplant) to evaluate potential donors for mismatch in HLA alleles (eg, HLA-DR8 versus HLA-DR3), which is associated with higher rates of posttransplant complications (eg, graft versus host disease, graft failure). An **HLA-identical sibling donor** would drastically reduce the likelihood of serious complications and increase the likelihood of a **successful transplant**.

Educational objective:

The human leukocyte antigen (HLA) genes encode major histocompatibility complex (MHC) molecules that are key to activation of the immune system in response to foreign (non-self) antigens. All the HLA genes are clustered together, meaning that there is a low rate of crossover and that offspring essentially inherit 2 HLA haplotypes, one from each parent. Therefore, the probability that a sibling would be an identical HLA match is 1/4.

Genetics	Genetics (General Principles)	Genetic inheritance
Subject	System	Topic

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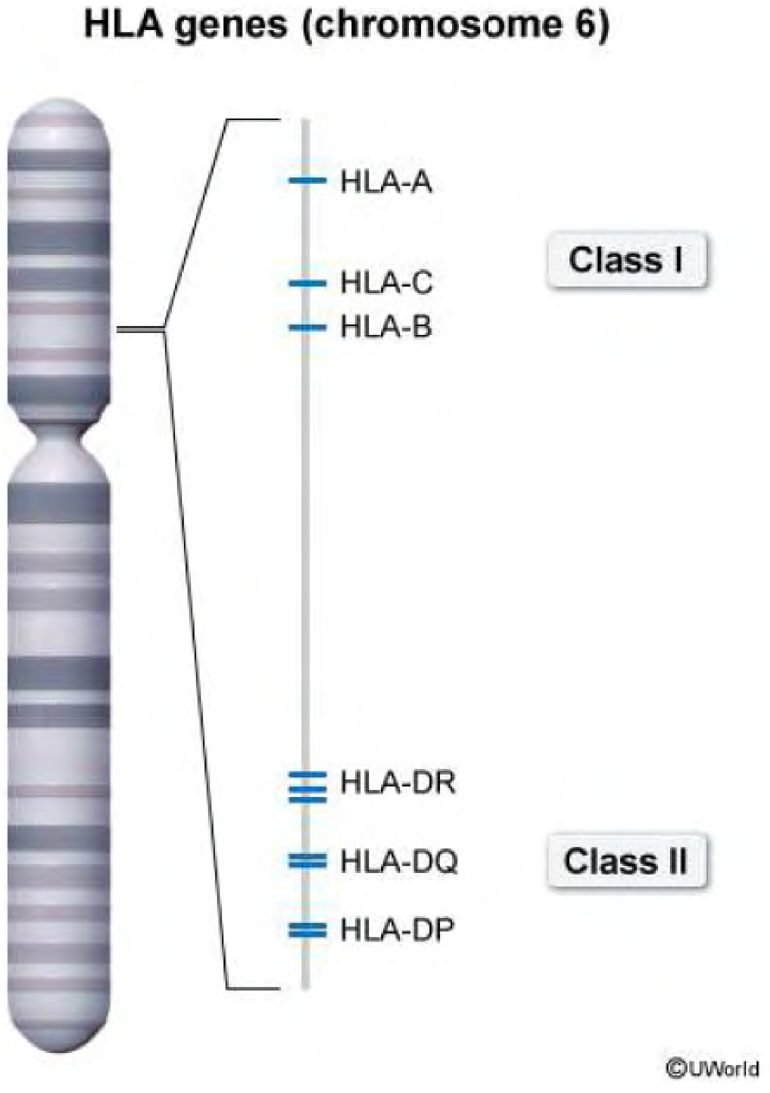
HLA genes (chromosome 6)
HLA-A
HLA-C
HLA-B
Class I
HLA-DR
HLA-DQ
HLA-DP
Class II
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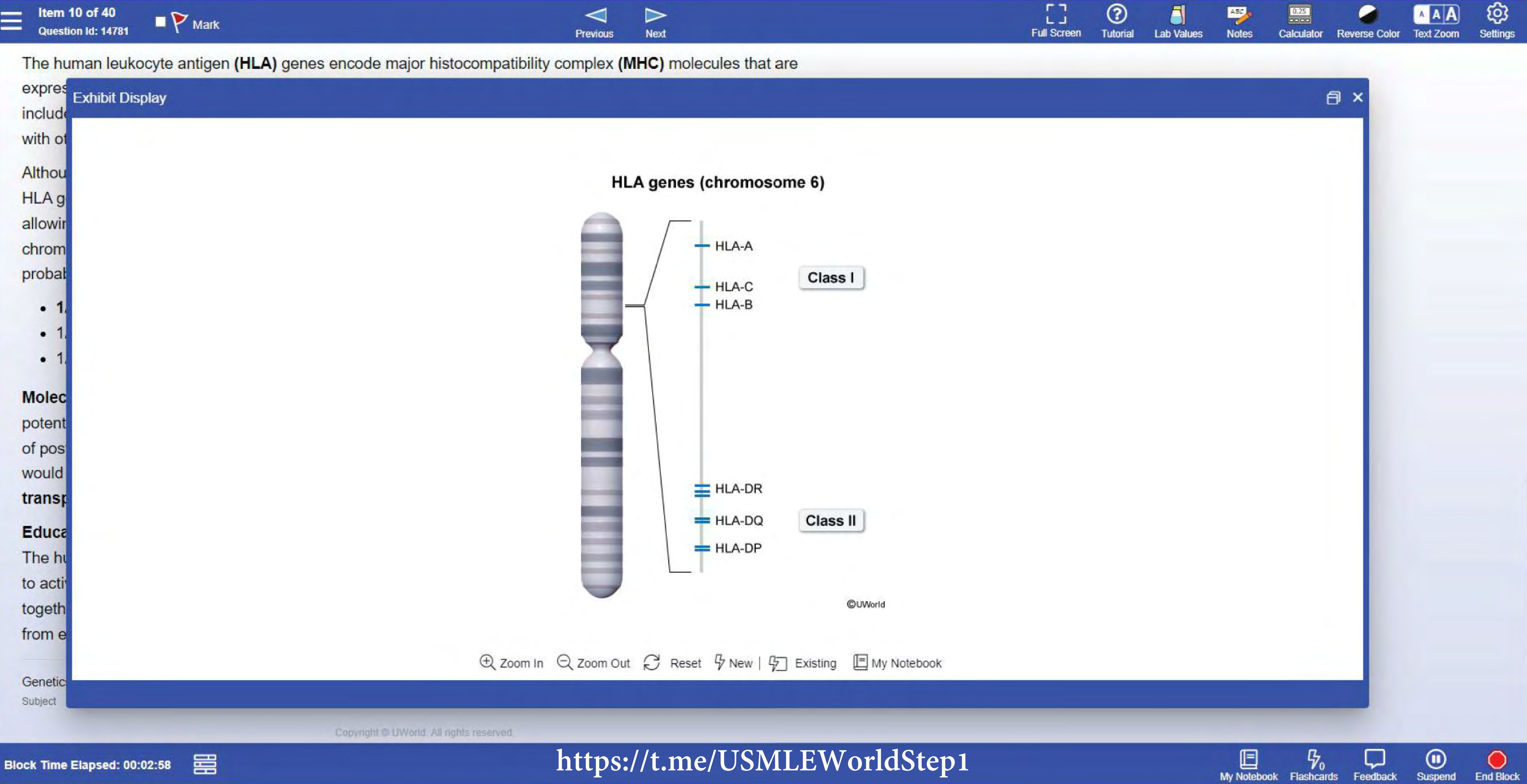
Item 10 of 40
Question Id: 14781
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
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The human leukocyte antigen **(HLA)** genes encode major histocompatibility complex **(MHC)** molecules that are

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HLA genes (chromosome 6)

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HLA-C
HLA-B
Class I
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HLA-DP
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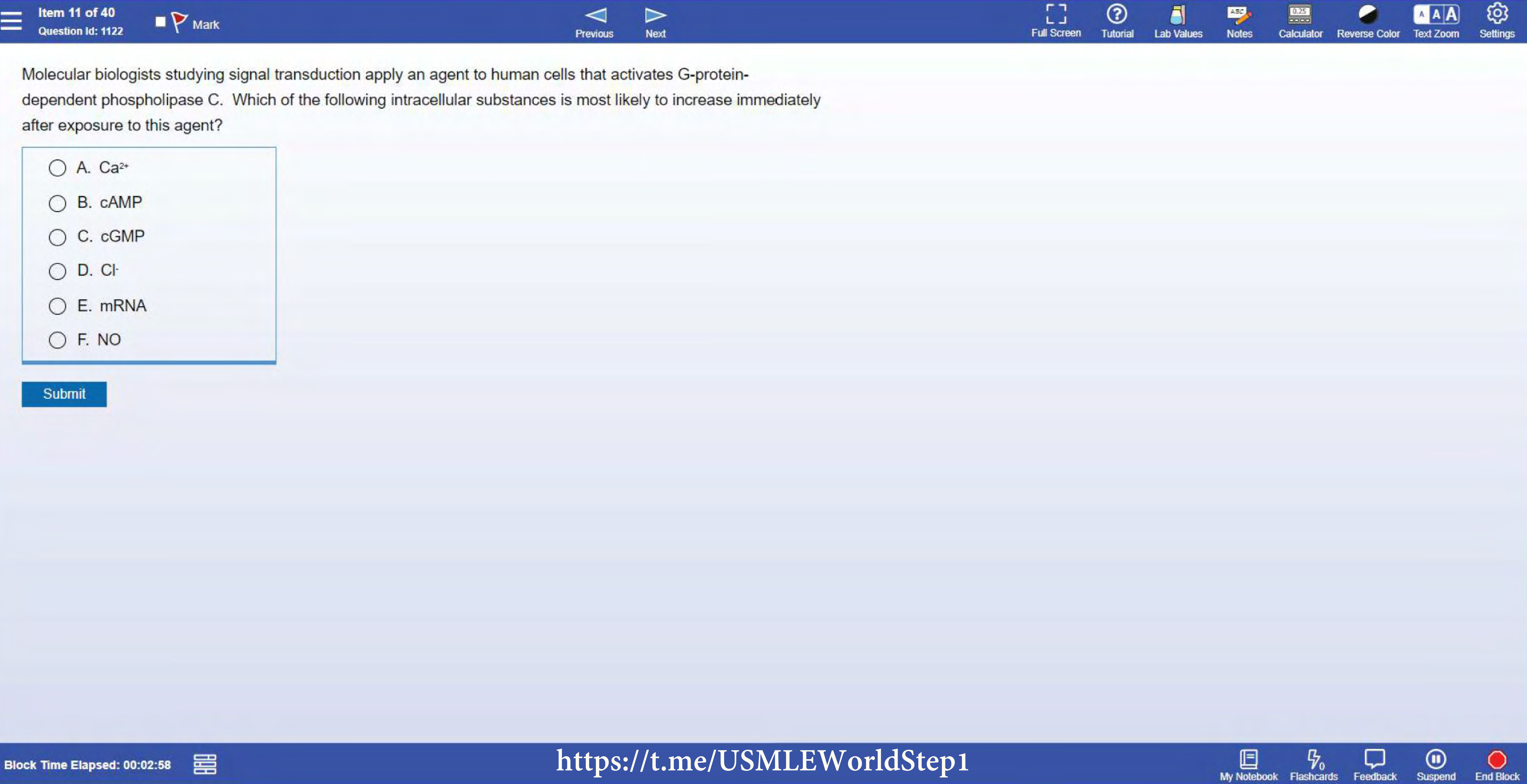
Item 11 of 40
Question Id: 1122
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein-dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

○ A. Ca^{2+}
○ B. cAMP
○ C. cGMP
○ D. Cl^-
○ E. mRNA
○ F. NO

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Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein-dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

✓ ○ A. Ca^{2+} (77%)
✗ ● B. cAMP (10%)
○ C. cGMP (9%)
○ D. Cl^- (0%)
○ E. mRNA (0%)
○ F. NO (1%)

Incorrect
Correct answer
A

77%
Answered correctly

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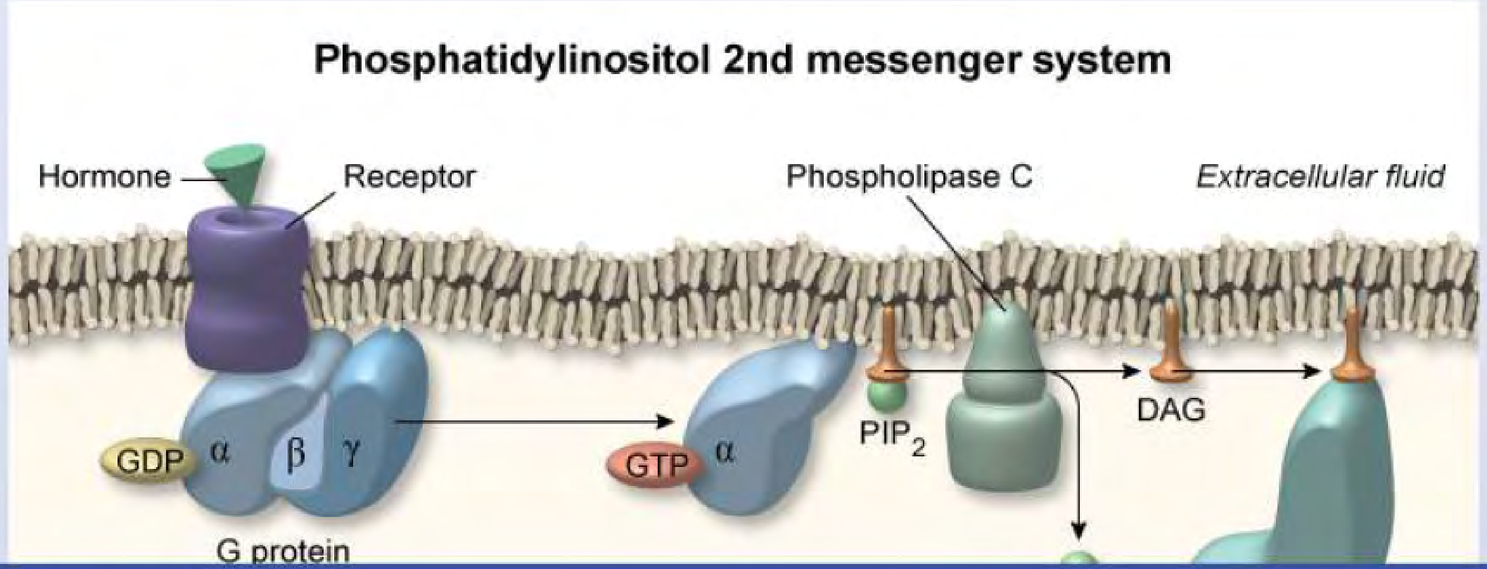
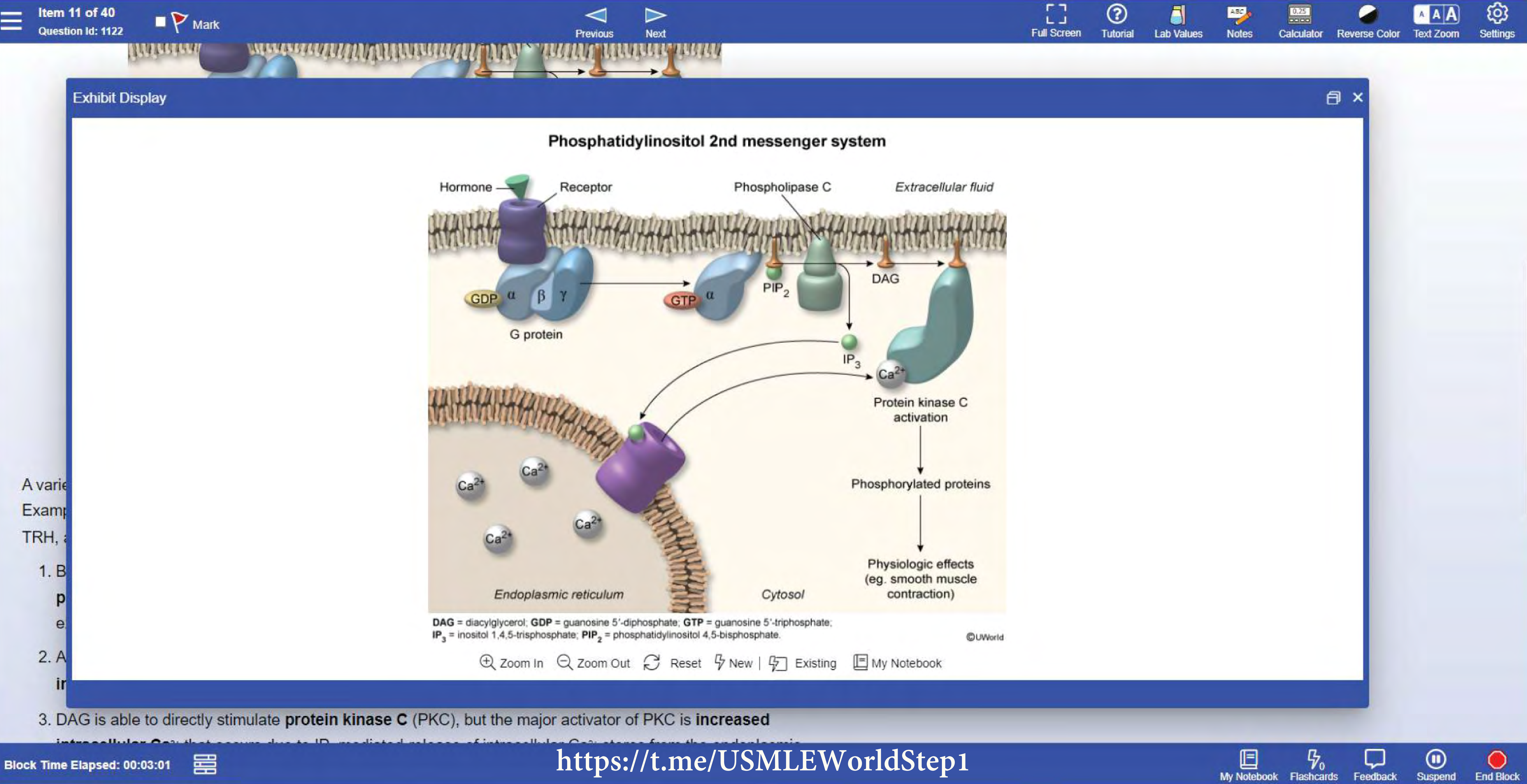
Explanation


Phosphatidylinositol 2nd messenger system
Hormone
Receptor
Phospholipase C
Extracellular fluid
GDP
α
β
γ
GTP
α
PIP2
DAG
G protein


Item 11 of 40
Question Id: 1122
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Hormone
Receptor
Phospholipase C
Extracellular fluid
GDP
α
β
γ
G protein
GTP
α
PIP_2
DAG
IP_3
Ca^{2+}
Protein kinase C activation
Phosphorylated proteins
Physiologic effects (eg. smooth muscle contraction)
Endoplasmic reticulum
Cytosol
Ca^{2+}
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Zoom Out
Reset
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My Notebook
Flashcards
Feedback
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Phosphatidylinositol 2nd messenger system

DAG = diacylglycerol; **GDP** = guanosine 5′-diphosphate; **GTP** = guanosine 5′-triphosphate; **IP_3** = inositol 1,4,5-trisphosphate; **PIP_2** = phosphatidylinositol 4,5-bisphosphate.

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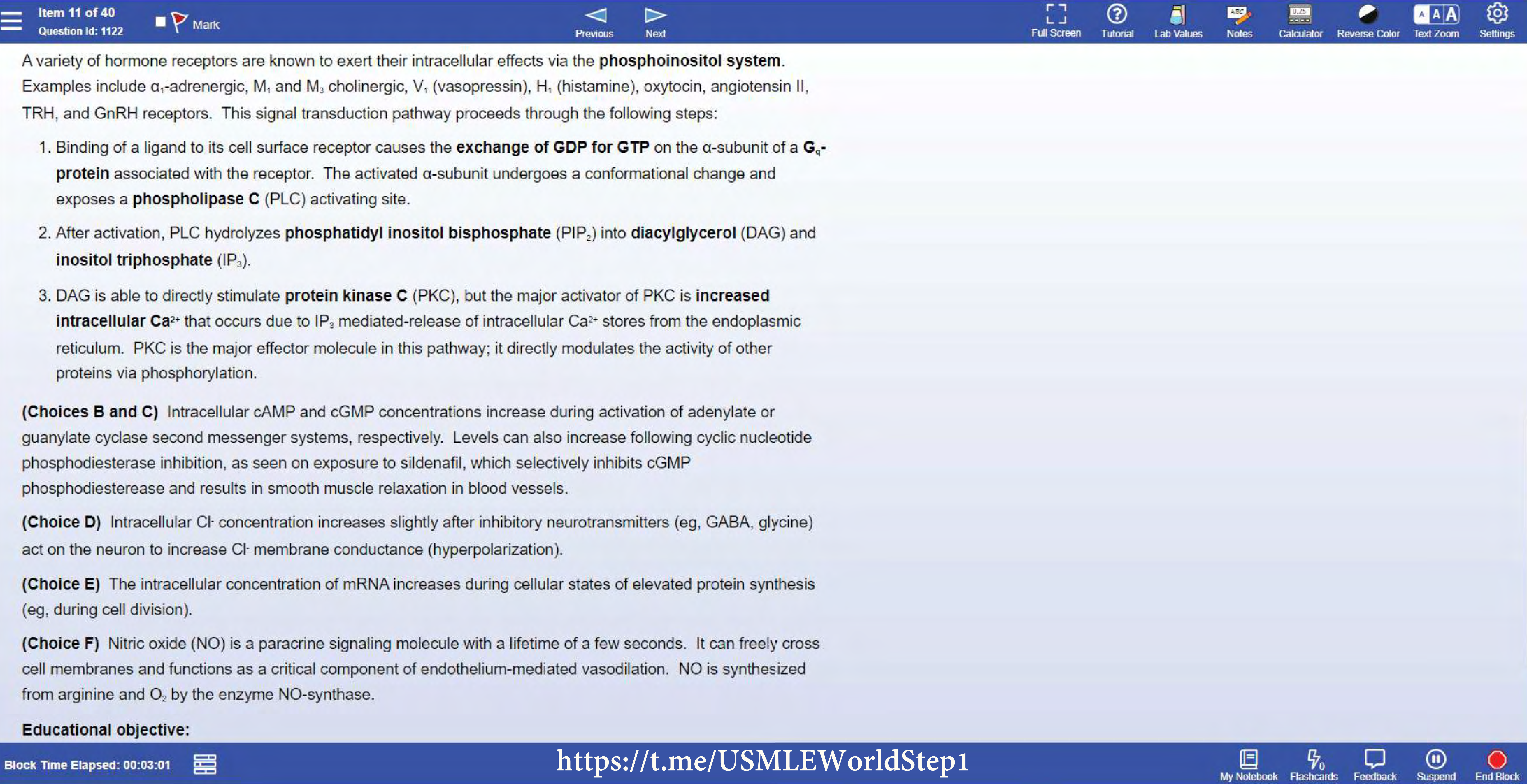
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3-mediated release of intracellular Ca^{2+} stores from the endoplasmic



A variety of hormone receptors are known to exert their intracellular effects via the **phosphoinositol system**. Examples include α_1-adrenergic, M_1 and M_3 cholinergic, V_1 (vasopressin), H_1 (histamine), oxytocin, angiotensin II, TRH, and GnRH receptors. This signal transduction pathway proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the **exchange of GDP for GTP** on the α-subunit of a **G_q-protein** associated with the receptor. The activated α-subunit undergoes a conformational change and exposes a **phospholipase C** (PLC) activating site.
2. After activation, PLC hydrolyzes **phosphatidyl inositol bisphosphate** (PIP_2) into **diacylglycerol** (DAG) and **inositol triphosphate** (IP_3).
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3 mediated-release of intracellular Ca^{2+} stores from the endoplasmic reticulum. PKC is the major effector molecule in this pathway; it directly modulates the activity of other proteins via phosphorylation.

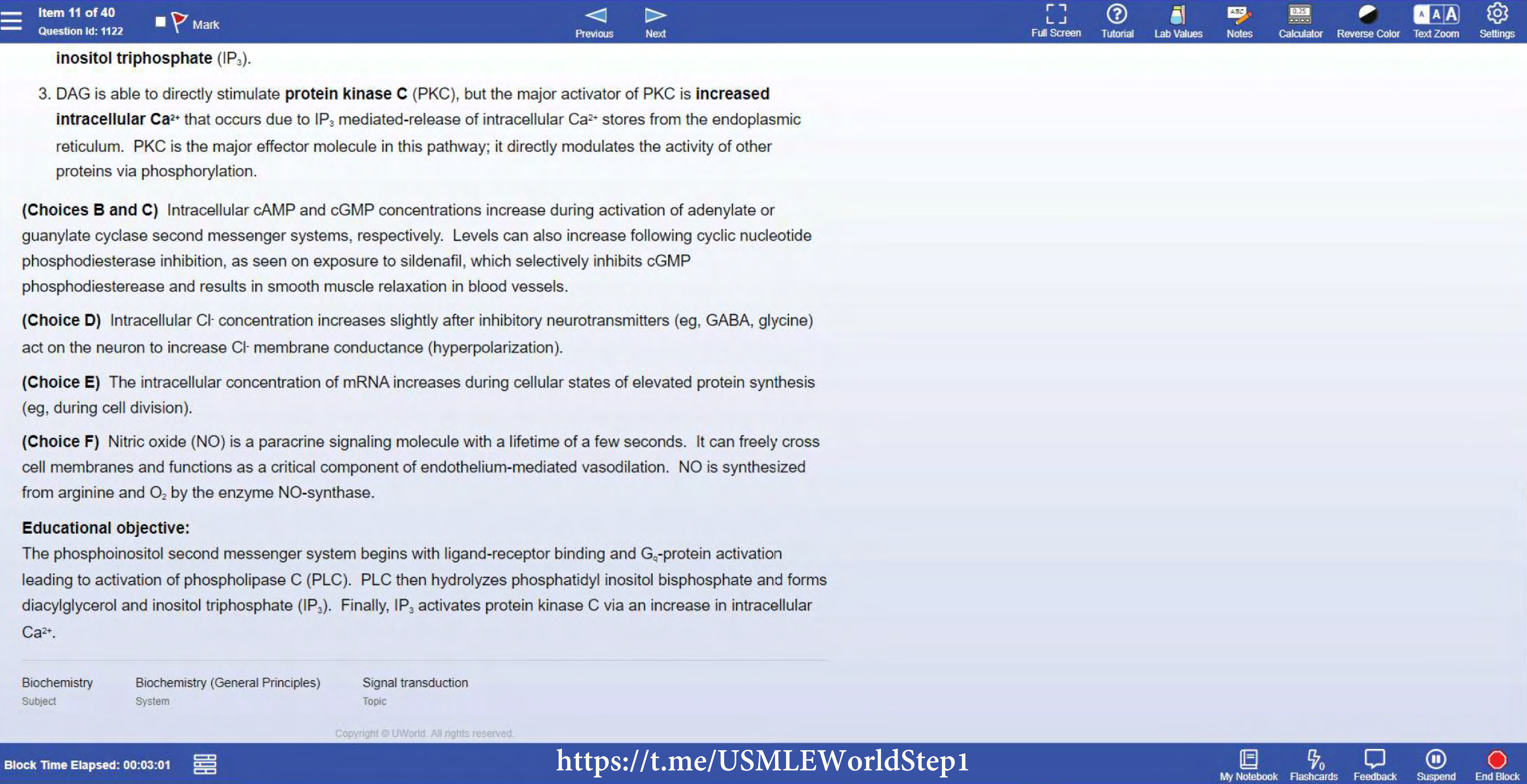
(Choices B and C) Intracellular cAMP and cGMP concentrations increase during activation of adenylate or guanylate cyclase second messenger systems, respectively. Levels can also increase following cyclic nucleotide phosphodiesterase inhibition, as seen on exposure to sildenafil, which selectively inhibits cGMP phosphodiesterease and results in smooth muscle relaxation in blood vessels.

(Choice D) Intracellular Cl^- concentration increases slightly after inhibitory neurotransmitters (eg, GABA, glycine) act on the neuron to increase Cl^- membrane conductance (hyperpolarization).

(Choice E) The intracellular concentration of mRNA increases during cellular states of elevated protein synthesis (eg, during cell division).

(Choice F) Nitric oxide (NO) is a paracrine signaling molecule with a lifetime of a few seconds. It can freely cross cell membranes and functions as a critical component of endothelium-mediated vasodilation. NO is synthesized from arginine and O_2 by the enzyme NO-synthase.

Educational objective:


Item 11 of 40
Question Id: 1122
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

inositol triphosphate (IP_3).

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Educational objective:

The phosphoinositol second messenger system begins with ligand-receptor binding and G_q-protein activation leading to activation of phospholipase C (PLC). PLC then hydrolyzes phosphatidyl inositol bisphosphate and forms diacylglycerol and inositol triphosphate (IP_3). Finally, IP_3 activates protein kinase C via an increase in intracellular Ca^{2+}.

Biochemistry	Biochemistry (General Principles)	Signal transduction
Subject	System	Topic

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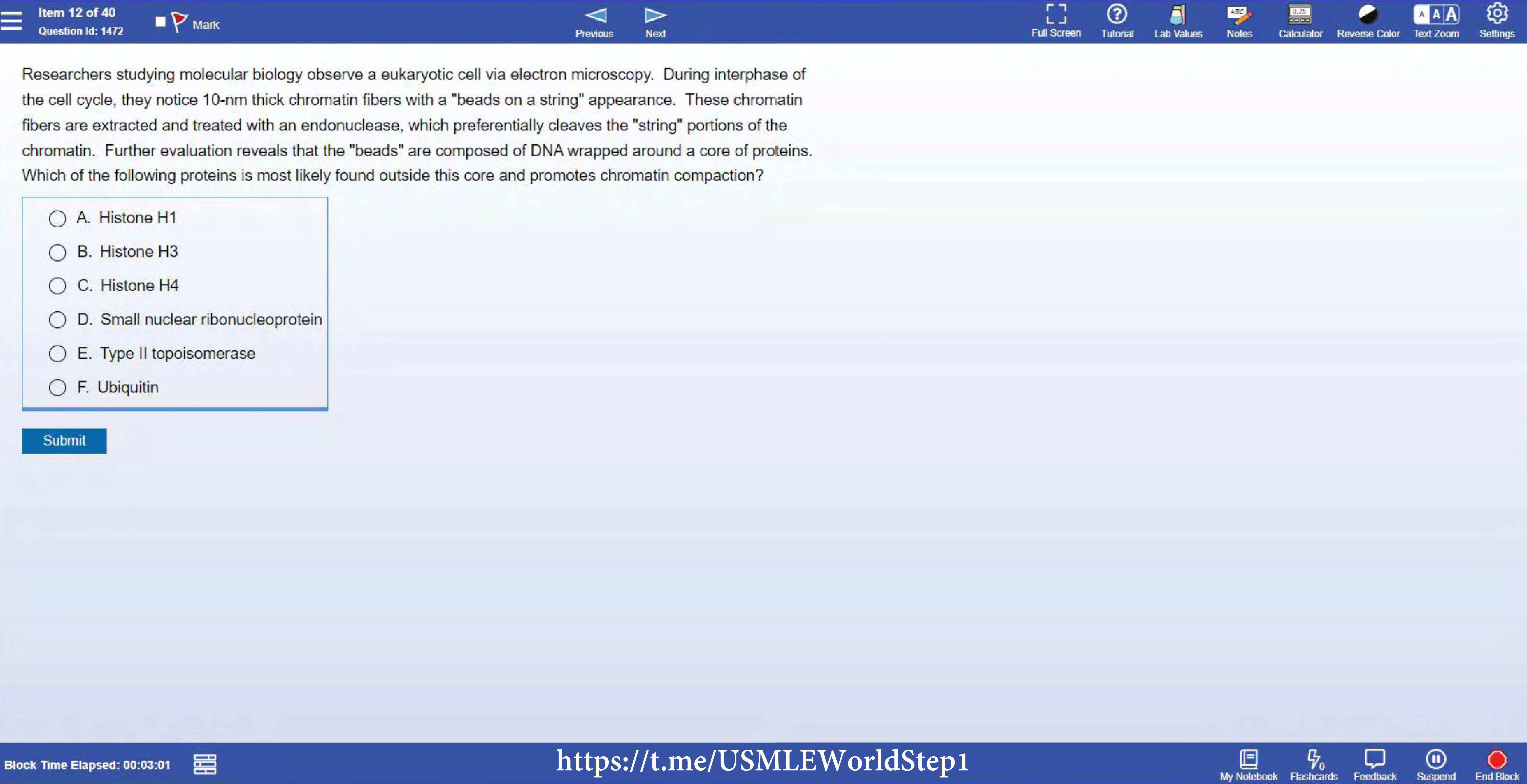
Item 12 of 40
Question Id: 1472
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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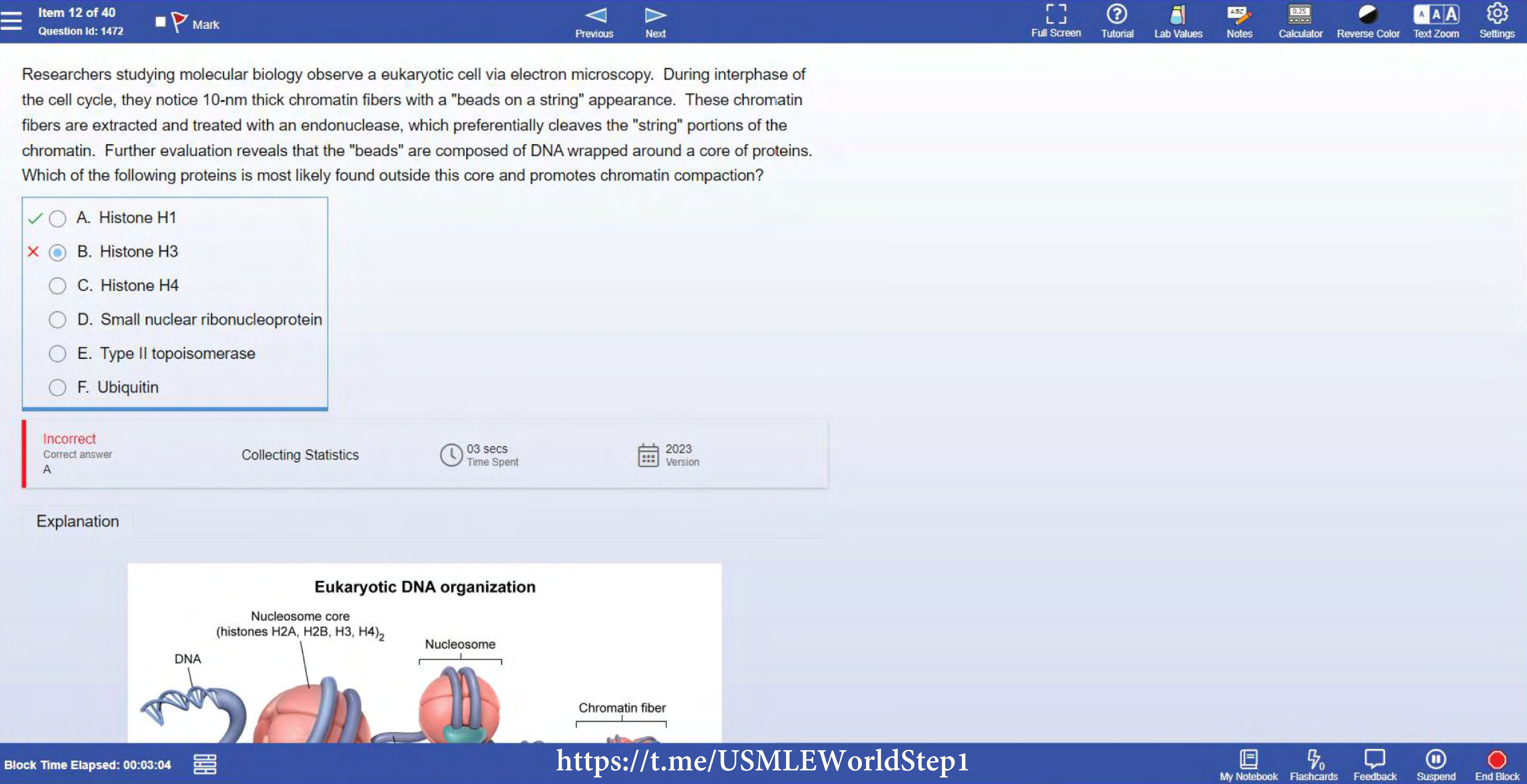
Block Time Elapsed: 00:03:01
My Notebook
Flashcards
Feedback
Suspend
End Block

Researchers studying molecular biology observe a eukaryotic cell via electron microscopy. During interphase of the cell cycle, they notice 10-nm thick chromatin fibers with a "beads on a string" appearance. These chromatin fibers are extracted and treated with an endonuclease, which preferentially cleaves the "string" portions of the chromatin. Further evaluation reveals that the "beads" are composed of DNA wrapped around a core of proteins. Which of the following proteins is most likely found outside this core and promotes chromatin compaction?

○ A. Histone H1
○ B. Histone H3
○ C. Histone H4
○ D. Small nuclear ribonucleoprotein
○ E. Type II topoisomerase
○ F. Ubiquitin


Item 12 of 40
Question Id: 1472
Mark
Previous
Next
Full Screen
Tutorial
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Calculator
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Text Zoom
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○ C. Histone H4

○ D. Small nuclear ribonucleoprotein

○ E. Type II topoisomerase

○ F. Ubiquitin

Incorrect
Correct answer
A

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2023
Version

Explanation

Eukaryotic DNA organization

Nucleosome core
(histones H2A, H2B, H3, H4)$_2$
DNA
Nucleosome
Chromatin fiber
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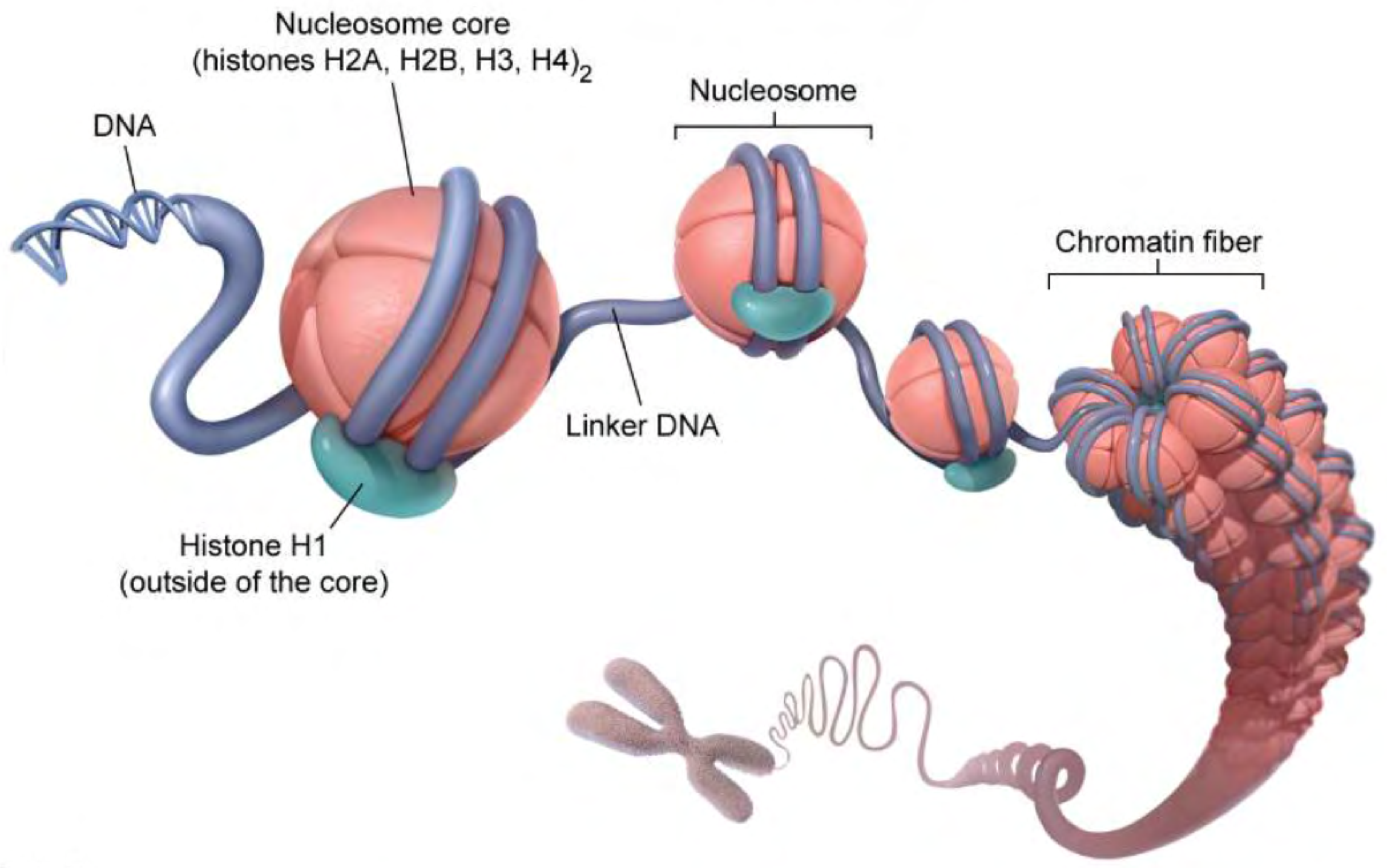
Eukaryotic DNA organization


Nucleosome core
(histones H2A, H2B, H3, H4)$_2$
DNA
Nucleosome
Chromatin fiber
Linker DNA
Histone H1
(outside of the core)

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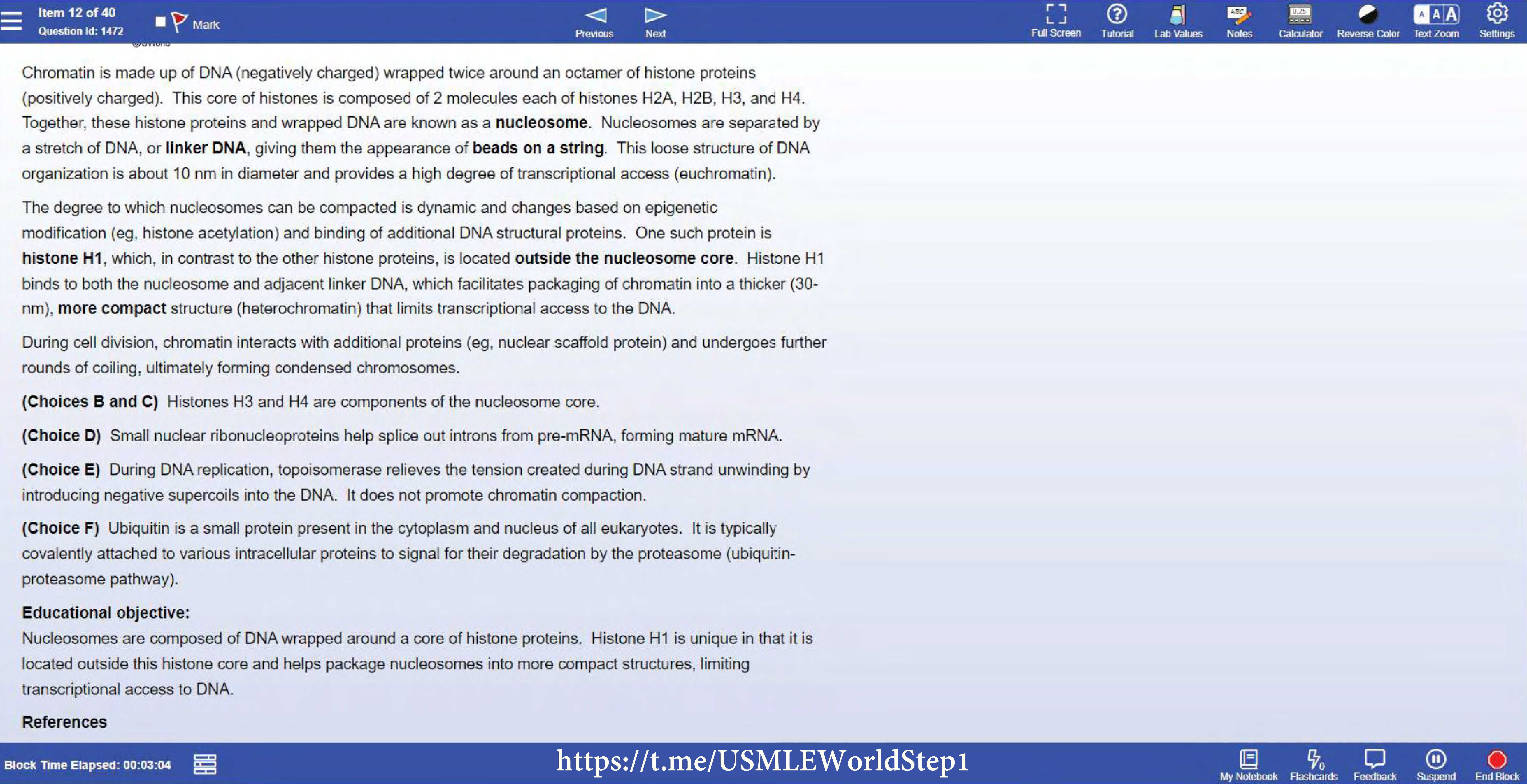
The degree to which nucleosomes can be compacted is dynamic and changes based on epigenetic modification (eg, histone acetylation) and binding of additional DNA structural proteins. One such protein is



Chromatin is made up of DNA (negatively charged) wrapped twice around an octamer of histone proteins (positively charged). This core of histones is composed of 2 molecules each of histones H2A, H2B, H3, and H4. Together, these histone proteins and wrapped DNA are known as a **nucleosome**. Nucleosomes are separated by a stretch of DNA, or **linker DNA**, giving them the appearance of **beads on a string**. This loose structure of DNA organization is about 10 nm in diameter and provides a high degree of transcriptional access (euchromatin).

The degree to which nucleosomes can be compacted is dynamic and changes based on epigenetic modification (eg, histone acetylation) and binding of additional DNA structural proteins. One such protein is **histone H1**, which, in contrast to the other histone proteins, is located **outside the nucleosome core**. Histone H1 binds to both the nucleosome and adjacent linker DNA, which facilitates packaging of chromatin into a thicker (30-nm), **more compact** structure (heterochromatin) that limits transcriptional access to the DNA.

During cell division, chromatin interacts with additional proteins (eg, nuclear scaffold protein) and undergoes further rounds of coiling, ultimately forming condensed chromosomes.

(Choices B and C) Histones H3 and H4 are components of the nucleosome core.

(Choice D) Small nuclear ribonucleoproteins help splice out introns from pre-mRNA, forming mature mRNA.

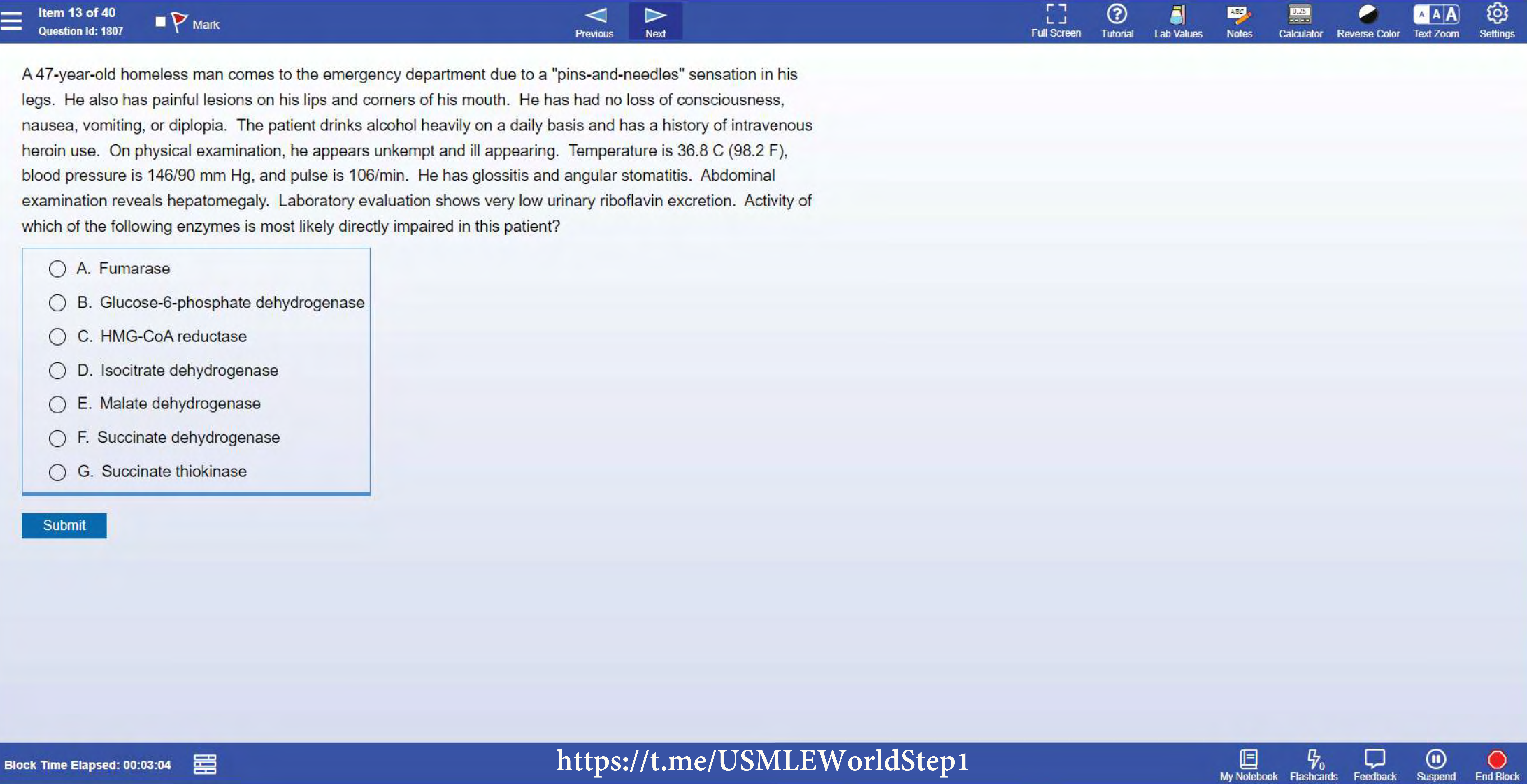
(Choice E) During DNA replication, topoisomerase relieves the tension created during DNA strand unwinding by introducing negative supercoils into the DNA. It does not promote chromatin compaction.

(Choice F) Ubiquitin is a small protein present in the cytoplasm and nucleus of all eukaryotes. It is typically covalently attached to various intracellular proteins to signal for their degradation by the proteasome (ubiquitin-proteasome pathway).

Educational objective:

Nucleosomes are composed of DNA wrapped around a core of histone proteins. Histone H1 is unique in that it is located outside this histone core and helps package nucleosomes into more compact structures, limiting transcriptional access to DNA.

References


Item 13 of 40
Question Id: 1807
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 47-year-old homeless man comes to the emergency department due to a "pins-and-needles" sensation in his legs. He also has painful lesions on his lips and corners of his mouth. He has had no loss of consciousness, nausea, vomiting, or diplopia. The patient drinks alcohol heavily on a daily basis and has a history of intravenous heroin use. On physical examination, he appears unkempt and ill appearing. Temperature is 36.8 C (98.2 F), blood pressure is 146/90 mm Hg, and pulse is 106/min. He has glossitis and angular stomatitis. Abdominal examination reveals hepatomegaly. Laboratory evaluation shows very low urinary riboflavin excretion. Activity of which of the following enzymes is most likely directly impaired in this patient?

○ A. Fumarase
○ B. Glucose-6-phosphate dehydrogenase
○ C. HMG-CoA reductase
○ D. Isocitrate dehydrogenase
○ E. Malate dehydrogenase
○ F. Succinate dehydrogenase
○ G. Succinate thiokinase

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My Notebook
Flashcards
Feedback
Suspend
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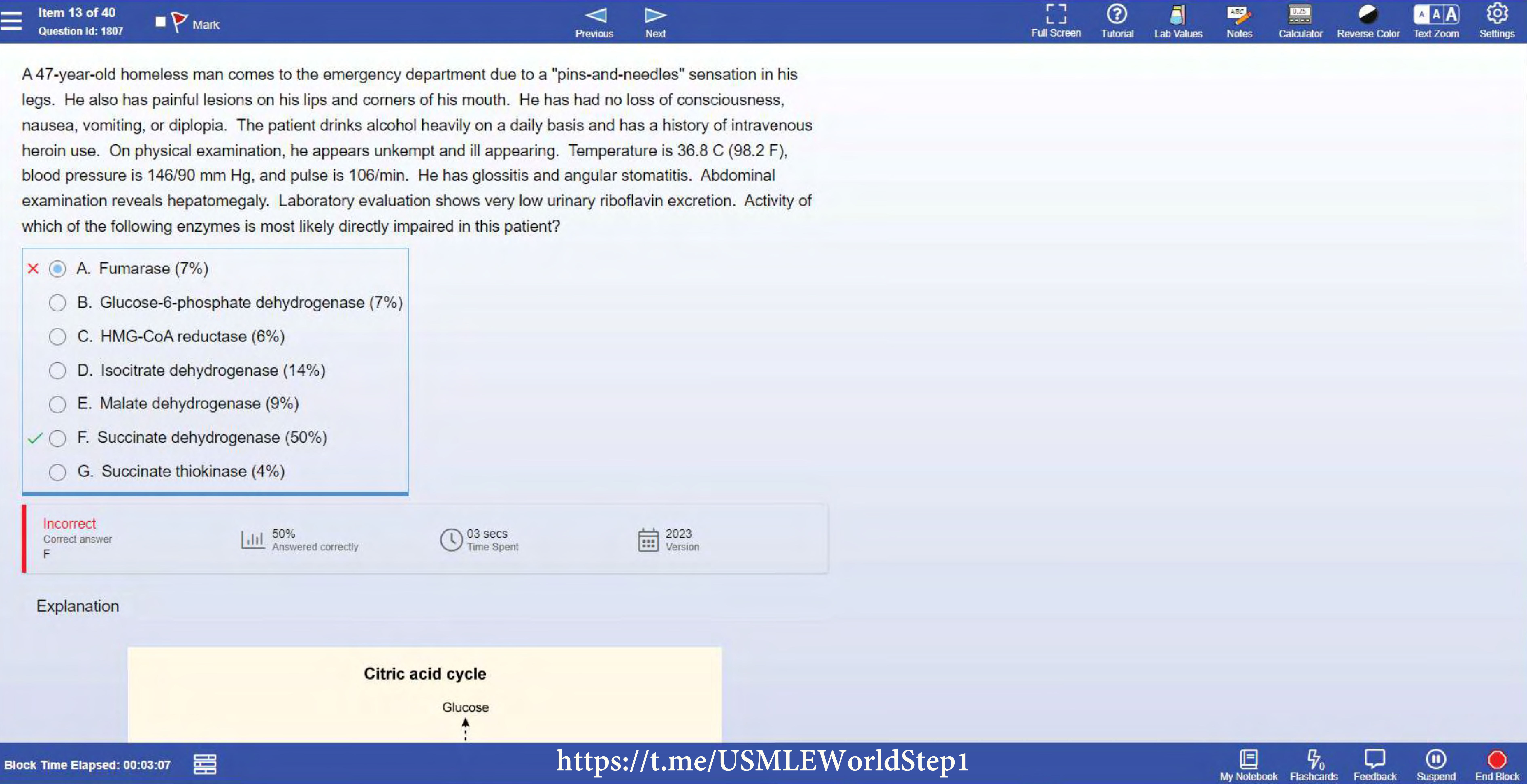
Item 13 of 40
Question Id: 1807
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 47-year-old homeless man comes to the emergency department due to a "pins-and-needles" sensation in his legs. He also has painful lesions on his lips and corners of his mouth. He has had no loss of consciousness, nausea, vomiting, or diplopia. The patient drinks alcohol heavily on a daily basis and has a history of intravenous heroin use. On physical examination, he appears unkempt and ill appearing. Temperature is 36.8 C (98.2 F), blood pressure is 146/90 mm Hg, and pulse is 106/min. He has glossitis and angular stomatitis. Abdominal examination reveals hepatomegaly. Laboratory evaluation shows very low urinary riboflavin excretion. Activity of which of the following enzymes is most likely directly impaired in this patient?

✗ ● A. Fumarase (7%)
○ B. Glucose-6-phosphate dehydrogenase (7%)
○ C. HMG-CoA reductase (6%)
○ D. Isocitrate dehydrogenase (14%)
○ E. Malate dehydrogenase (9%)
✓ ○ F. Succinate dehydrogenase (50%)
○ G. Succinate thiokinase (4%)

Incorrect
Correct answer
F

50%
Answered correctly

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Time Spent

2023
Version

Explanation

Citric acid cycle

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My Notebook
Flashcards
Feedback
Suspend
End Block

○ G. Succinate thiokinase (4%)

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F

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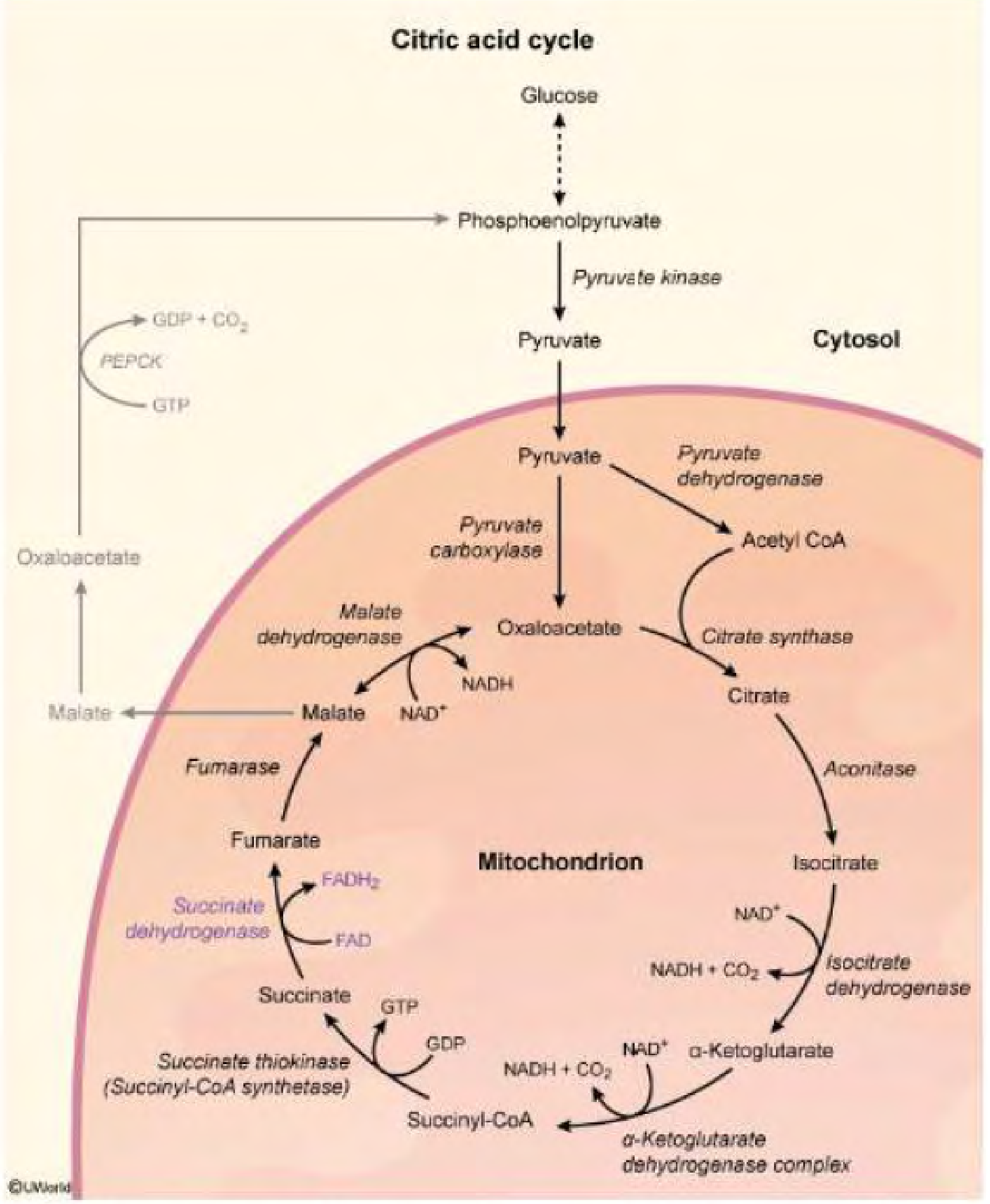
Citric acid cycle
Glucose
Phosphoenolpyruvate
Pyruvate kinase
GDP + CO$_2$
PEPCK
GTP
Pyruvate
Cytosol
Pyruvate
Pyruvate dehydrogenase
Acetyl CoA
Pyruvate carboxylase
Oxaloacetate
Malate dehydrogenase
Oxaloacetate
Citrate synthase
NADH
Malate
Malate
NAD$^+$
Citrate
Aconitase
Fumarase
Fumarate
Mitochondrion
Isocitrate
FADH$_2$
Succinate dehydrogenase
FAD
NAD$^+$
NADH + CO$_2$
Isocitrate dehydrogenase
Succinate
GTP
GDP
NAD$^+$
α-Ketoglutarate
NADH + CO$_2$
Succinate thiokinase (Succinyl-CoA synthetase)
Succinyl-CoA
α-Ketoglutarate dehydrogenase complex
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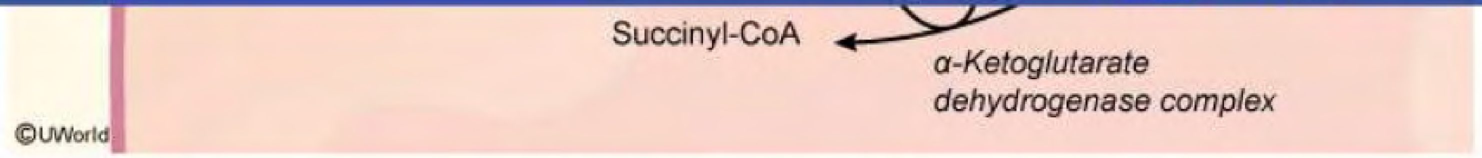
Fumarase
Aconitase
Fumarate



This patient's low urinary riboflavin excretion suggests a significant deficiency in riboflavin intake. Symptomatic **riboflavin deficiency** is rare in the United States but can be seen with chronic alcohol use and in severely malnourished patients. Clinical manifestations include angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

The **riboflavin** (vitamin B_2)-containing coenzymes are key constituents of the **electron transport chain**. Typically, riboflavin is first phosphorylated to become flavin mononucleotide (FMN), which can then be integrated into a coenzyme-flavin complex or further phosphorylated to flavin adenine dinucleotide (FAD). FMN and FAD participate as coenzymes in numerous reduction-oxidation reactions and are converted into reduced, energy-carrying states ($FMNH_2$ and $FADH_2$) through the acceptance of electrons.

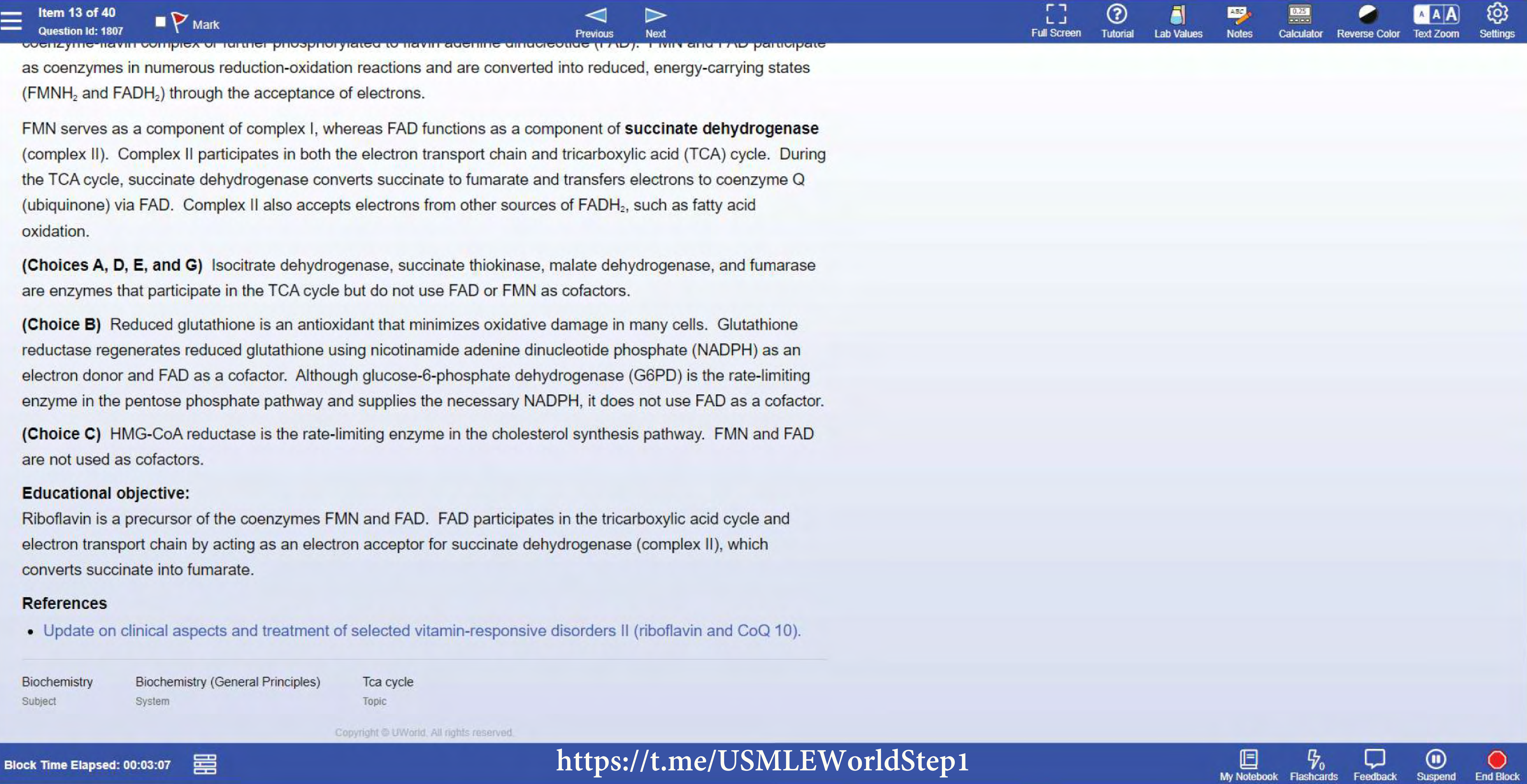
FMN serves as a component of complex I, whereas FAD functions as a component of **succinate dehydrogenase** (complex II). Complex II participates in both the electron transport chain and tricarboxylic acid (TCA) cycle. During the TCA cycle, succinate dehydrogenase converts succinate to fumarate and transfers electrons to coenzyme Q (ubiquinone) via FAD. Complex II also accepts electrons from other sources of $FADH_2$, such as fatty acid oxidation.

(Choices A, D, E, and G) Isocitrate dehydrogenase, succinate thiokinase, malate dehydrogenase, and fumarase are enzymes that participate in the TCA cycle but do not use FAD or FMN as cofactors.

(Choice B) Reduced glutathione is an antioxidant that minimizes oxidative damage in many cells. Glutathione reductase regenerates reduced glutathione using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and FAD as a cofactor. Although glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the pentose phosphate pathway and supplies the necessary NADPH, it does not use FAD as a cofactor.

(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:



coenzyme-flavin complex or further phosphorylated to flavin adenine dinucleotide (FAD). FMN and FAD participate as coenzymes in numerous reduction-oxidation reactions and are converted into reduced, energy-carrying states ($FMNH_2$ and $FADH_2$) through the acceptance of electrons.

FMN serves as a component of complex I, whereas FAD functions as a component of **succinate dehydrogenase** (complex II). Complex II participates in both the electron transport chain and tricarboxylic acid (TCA) cycle. During the TCA cycle, succinate dehydrogenase converts succinate to fumarate and transfers electrons to coenzyme Q (ubiquinone) via FAD. Complex II also accepts electrons from other sources of $FADH_2$, such as fatty acid oxidation.

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(Choice B) Reduced glutathione is an antioxidant that minimizes oxidative damage in many cells. Glutathione reductase regenerates reduced glutathione using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and FAD as a cofactor. Although glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the pentose phosphate pathway and supplies the necessary NADPH, it does not use FAD as a cofactor.

(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:

Riboflavin is a precursor of the coenzymes FMN and FAD. FAD participates in the tricarboxylic acid cycle and electron transport chain by acting as an electron acceptor for succinate dehydrogenase (complex II), which converts succinate into fumarate.

References

- Update on clinical aspects and treatment of selected vitamin-responsive disorders II (riboflavin and CoQ 10).

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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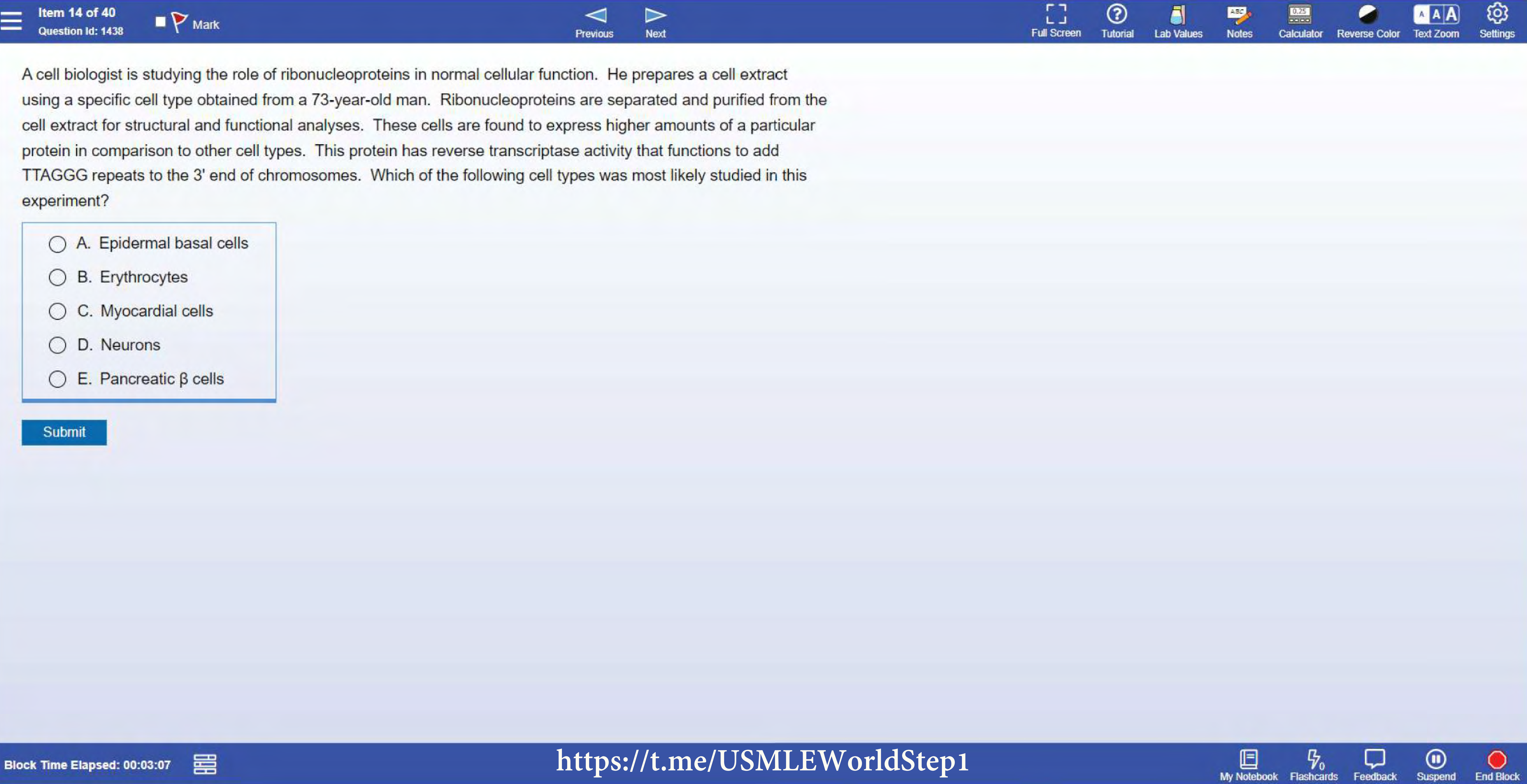
Item 14 of 40
Question Id: 1438
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

○ A. Epidermal basal cells
○ B. Erythrocytes
○ C. Myocardial cells
○ D. Neurons
○ E. Pancreatic β cells

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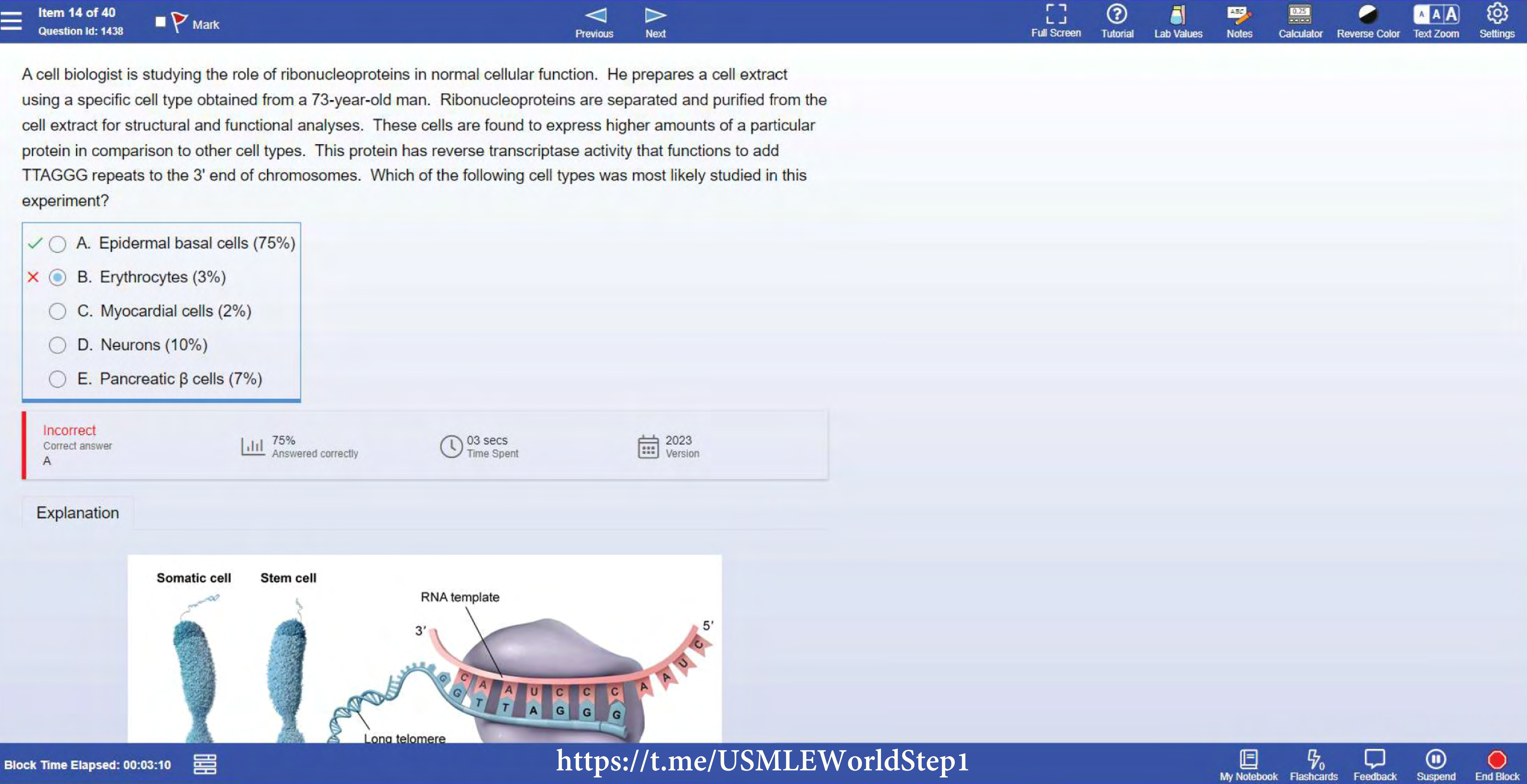
Item 14 of 40
Question Id: 1438
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

- ✓ ○ A. Epidermal basal cells (75%)
- ✗ ● B. Erythrocytes (3%)
- ○ C. Myocardial cells (2%)
- ○ D. Neurons (10%)
- ○ E. Pancreatic β cells (7%)

Incorrect
Correct answer
A

75%
Answered correctly

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2023
Version

Explanation

Somatic cell
Stem cell
RNA template
3'
5'
C A A U C C C A A U C
G T T A G G G
Long telomere

Block Time Elapsed: 00:03:10

My Notebook
Flashcards
Feedback
Suspend
End Block

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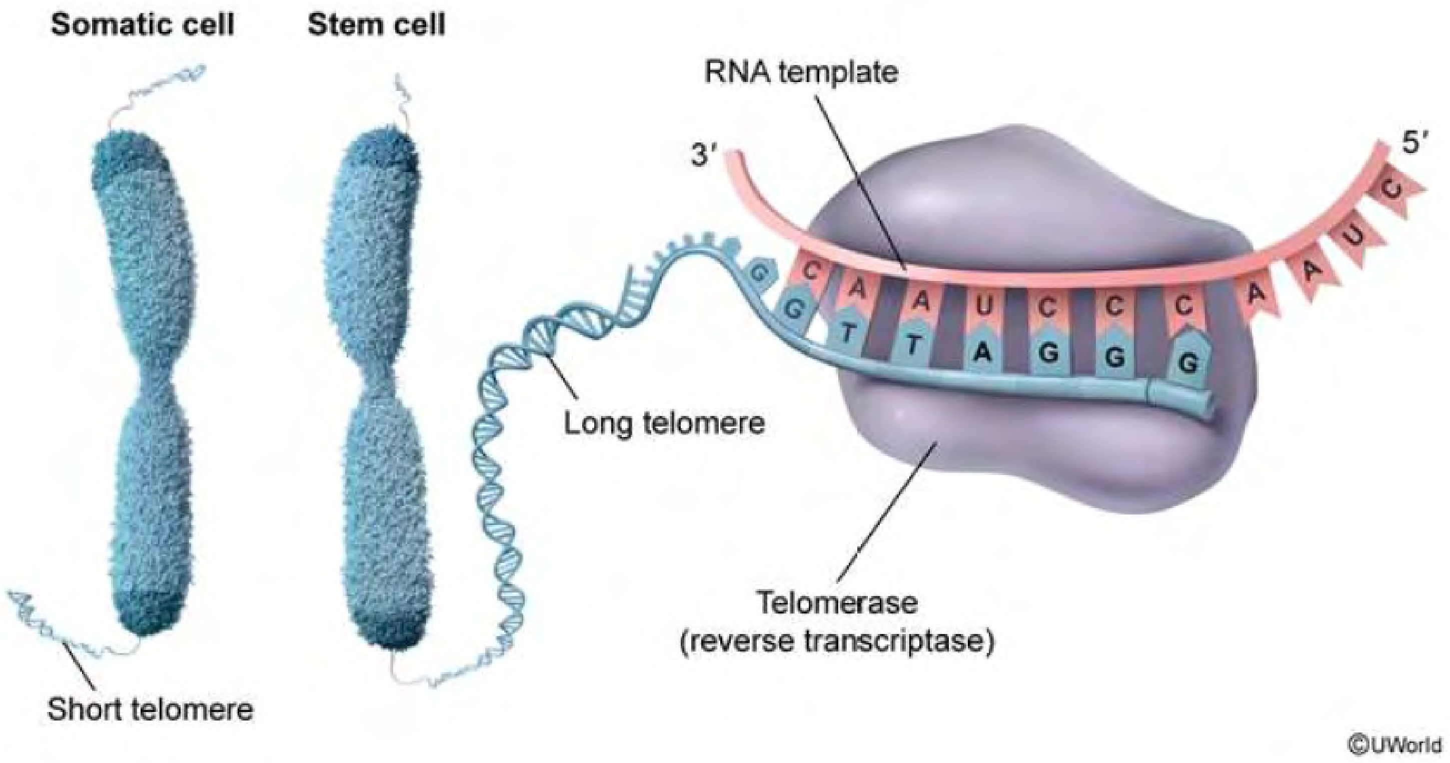
Somatic cell
Stem cell
RNA template
3′
5′
C A A U C C C A A U C
G G T T A G G G
Long telomere
Telomerase
(reverse transcriptase)
Short telomere
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My Notebook

Telom

It is si

RNA a

telome

in" RN

telome

Stem cells have very **long telomeres** due to their high telomerase activity, allowing them to proliferate indefinitely

Item 14 of 40
Question Id: 1438
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Telomerase is a ribonucleoprotein that adds **TTAGGG** repeats to the **3' end of chromosomes** (telomere region). It is similar to other reverse transcriptase enzymes in that it synthesizes single-stranded DNA using single-stranded RNA as a template (**RNA-dependent DNA polymerase**). Telomerase is composed of 2 main subunits, the telomerase reverse transcriptase (TERT) subunit and the telomerase RNA component (TERC). TERC is a "built-in" RNA template that is repeatedly read by the TERT subunit to add TTAGGG DNA sequence repeats to telomeres.

Stem cells have very **long telomeres** due to their high telomerase activity, allowing them to proliferate indefinitely in a controlled manner. In contrast, most terminally differentiated adult somatic cells (eg, myocardial cells, neurons, pancreatic β cells) have short telomeres as they do not express telomerase and their telomeres shorten with every cell division **(Choices C, D, and E)**. Critical shortening in telomere length is thought to be a signal for programmed cell death. In fact, syndromes of premature aging (eg, Bloom syndrome) are associated with shortened telomeres. In contrast, cancer cells upregulate their telomerase activity, preventing cell death by maintaining their telomere length.

Stem cells are undifferentiated cells with the potential to differentiate into other cell types and can be classified as either embryonic or adult stem cells. Although embryonic stem cells are present in the very early stages of embryogenesis and can give rise to every cell type in adult humans (pluripotent), adult stem cells are present in most tissues and are generally responsible for replacing dead cells. For example, the epidermis is continuously replaced by stem cells present in the basal cell layers. Bone marrow stem cells similarly replace peripheral red and white blood cells.

(Choice B) Erythrocytes have no nuclei and therefore have no potential to divide.

Educational objective:

Critical shortening in telomere length can signal for programmed cell death. Telomerase is a reverse transcriptase (RNA-dependent DNA polymerase) that lengthens telomeres by adding TTAGGG repeats to the 3' end of chromosomes. Stem cells have long telomeres due to high telomerase activity, allowing them to proliferate indefinitely in a controlled manner.

References

Item 15 of 40
Question Id: 21501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 9-month-old boy is brought to the clinic for a routine follow-up. His mother is concerned because the patient is not yet able to sit up unsupported. He was born at term and has had muscle weakness since birth. Vital signs are normal. The patient is alert but has diminished tone. Examination shows a prominent forehead with a depressed nasal bridge. Eye examination shows epicanthal folds. Analysis of lysosomal acid hydrolases shows an increased concentration within the serum and a decreased level within the cultured skin fibroblast cells. This patient most likely has a defect in which of the following steps of enzyme production?

○ A. DNA methylation
○ B. Posttranslational modification
○ C. Protein folding
○ D. Splicing
○ E. Translation

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My Notebook
Flashcards
Feedback
Suspend
End Block

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- ✗ ● A. DNA methylation (4%)
- ✓ ○ B. Posttranslational modification (72%)
- ○ C. Protein folding (13%)
- ○ D. Splicing (6%)
- ○ E. Translation (2%)

Incorrect
Correct answer
B

72%
Answered correctly

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Time Spent

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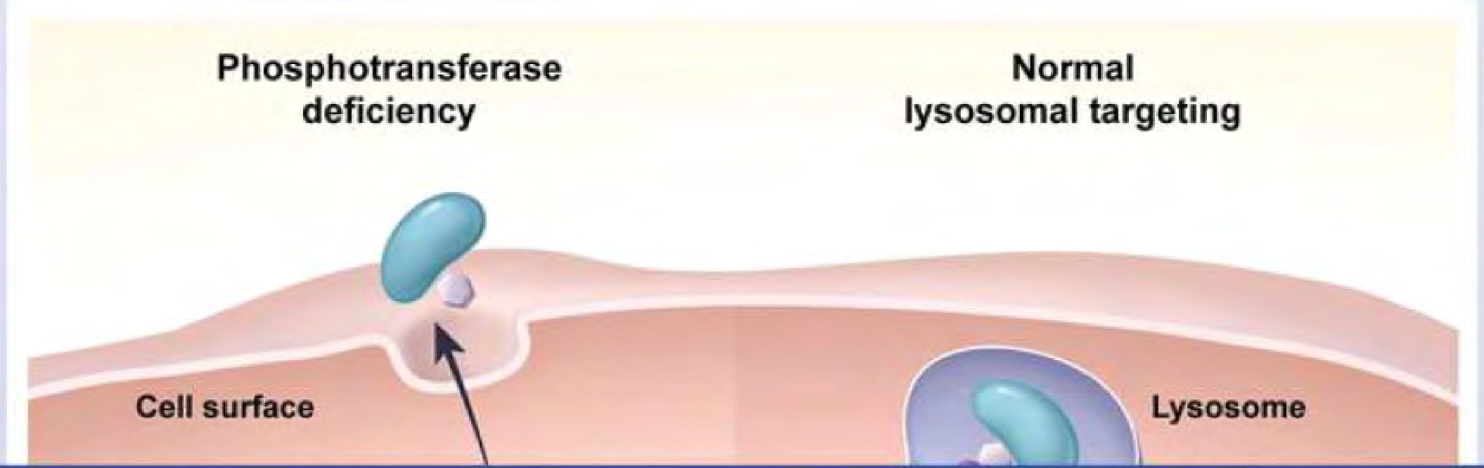
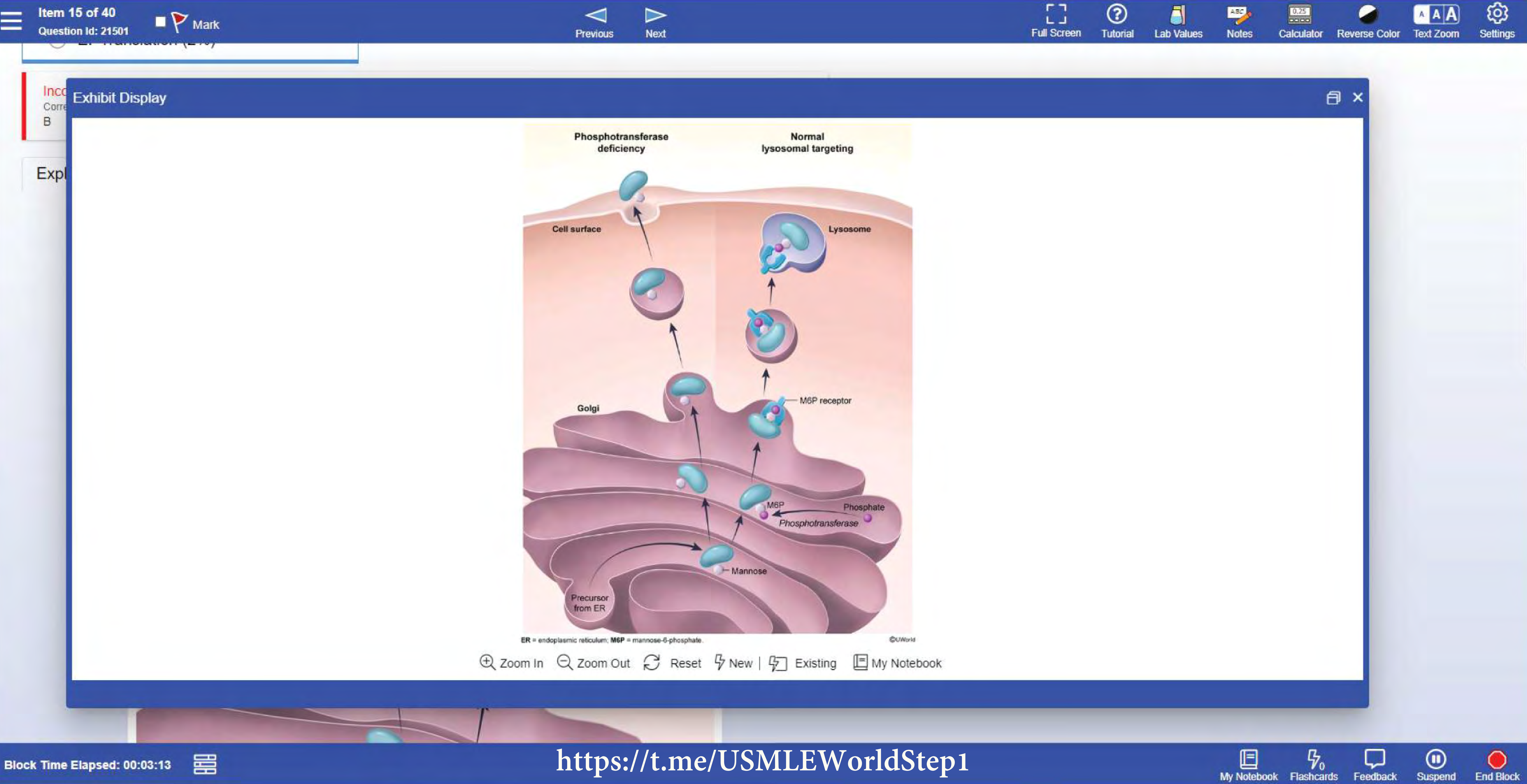
Version

Explanation





Item 15 of 40
Question Id: 21501
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Inco
Corre
B
Expl
Exhibit Display
Phosphotransferase deficiency
Normal lysosomal targeting
Cell surface
Lysosome
Golgi
M6P receptor
M6P
Phosphate
Phosphotransferase
Mannose
Precursor from ER
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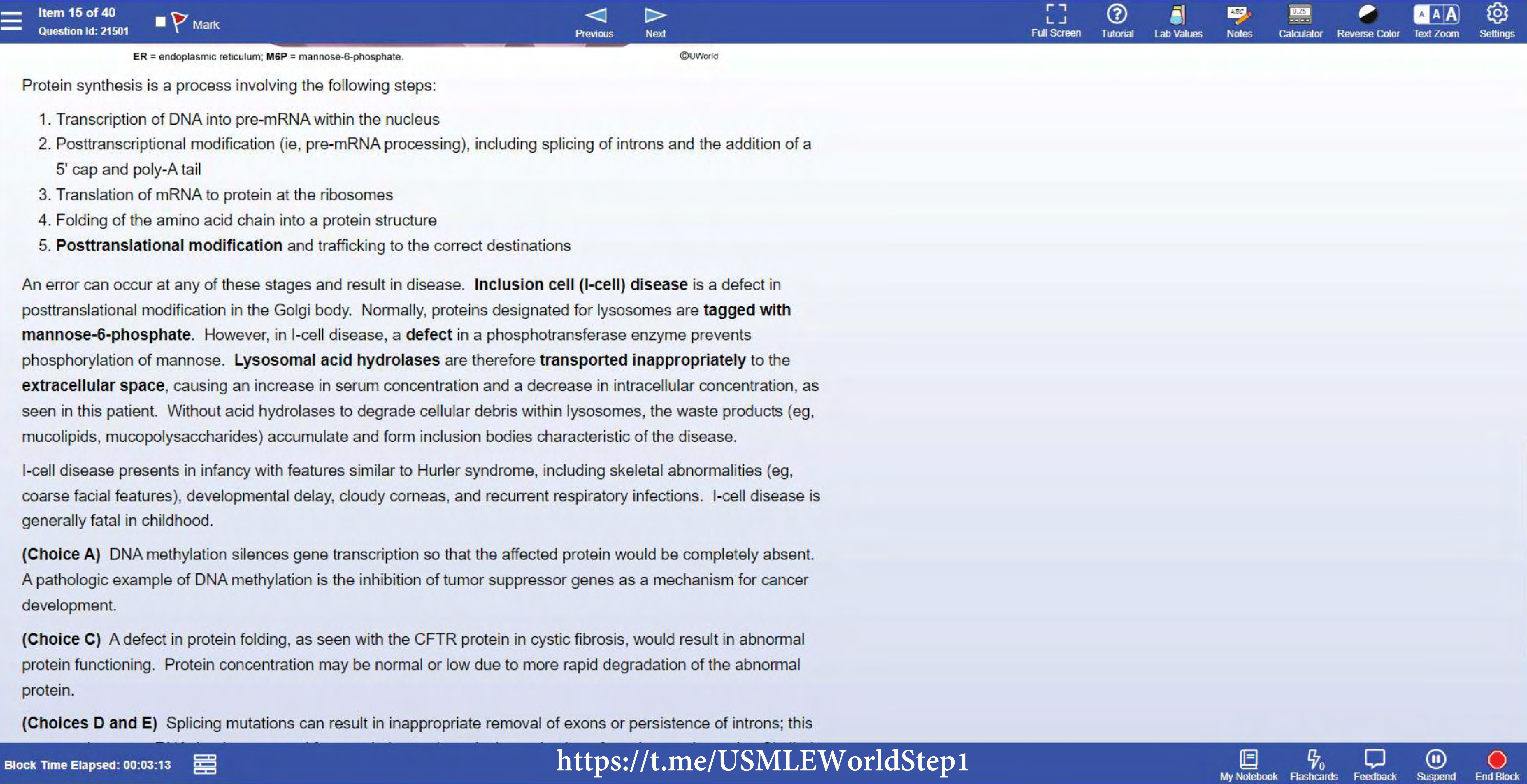
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Flashcards
Feedback
Suspend
End Block

ER = endoplasmic reticulum; **M6P** = mannose-6-phosphate.

Block Time Elapsed: 00:03:13



ER = endoplasmic reticulum; **M6P** = mannose-6-phosphate.

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Protein synthesis is a process involving the following steps:

1. Transcription of DNA into pre-mRNA within the nucleus
2. Posttranscriptional modification (ie, pre-mRNA processing), including splicing of introns and the addition of a 5' cap and poly-A tail
3. Translation of mRNA to protein at the ribosomes
4. Folding of the amino acid chain into a protein structure
5. **Posttranslational modification** and trafficking to the correct destinations

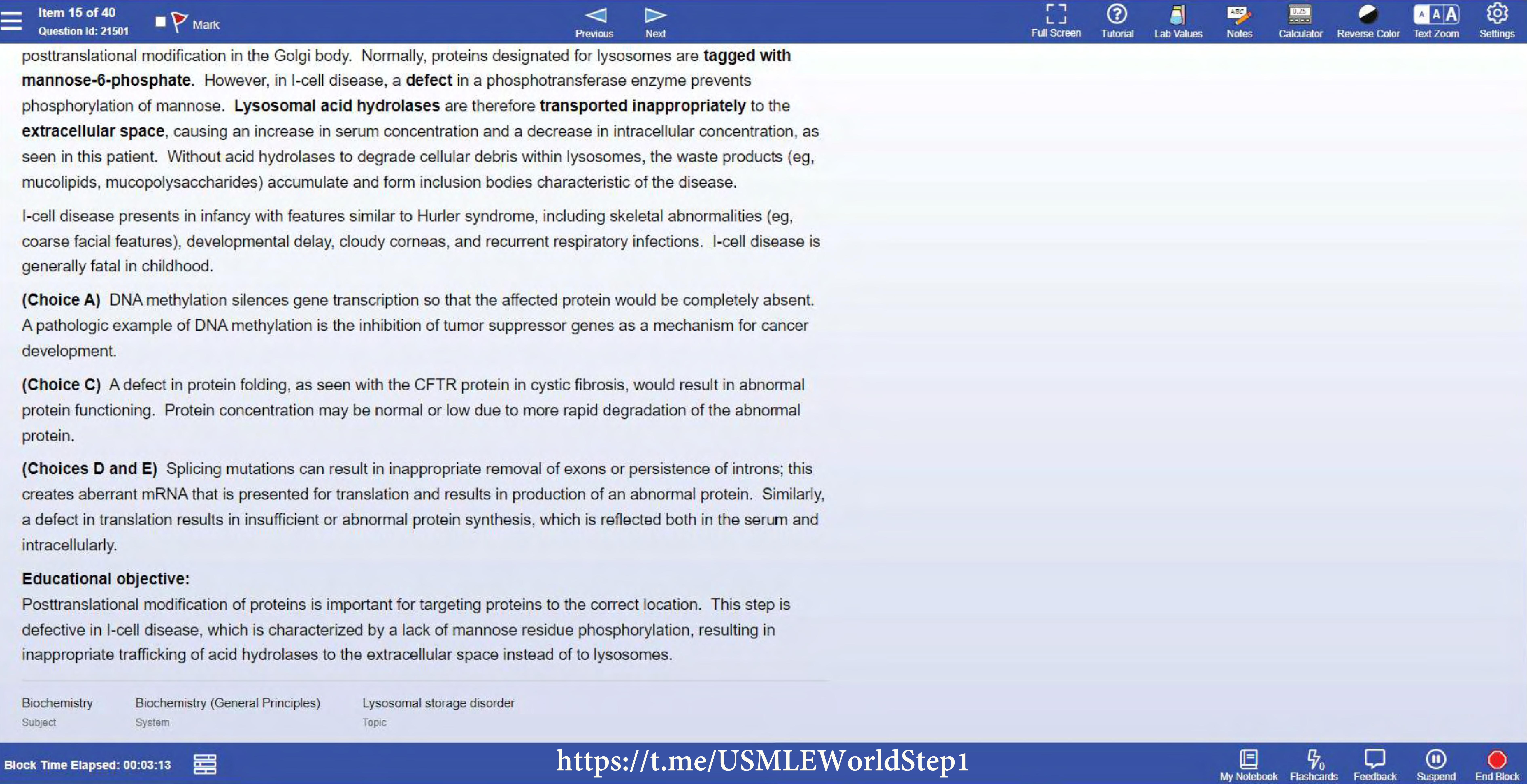
An error can occur at any of these stages and result in disease. **Inclusion cell (I-cell) disease** is a defect in posttranslational modification in the Golgi body. Normally, proteins designated for lysosomes are **tagged with mannose-6-phosphate**. However, in I-cell disease, a **defect** in a phosphotransferase enzyme prevents phosphorylation of mannose. **Lysosomal acid hydrolases** are therefore **transported inappropriately** to the **extracellular space**, causing an increase in serum concentration and a decrease in intracellular concentration, as seen in this patient. Without acid hydrolases to degrade cellular debris within lysosomes, the waste products (eg, mucolipids, mucopolysaccharides) accumulate and form inclusion bodies characteristic of the disease.

I-cell disease presents in infancy with features similar to Hurler syndrome, including skeletal abnormalities (eg, coarse facial features), developmental delay, cloudy corneas, and recurrent respiratory infections. I-cell disease is generally fatal in childhood.

(Choice A) DNA methylation silences gene transcription so that the affected protein would be completely absent. A pathologic example of DNA methylation is the inhibition of tumor suppressor genes as a mechanism for cancer development.

(Choice C) A defect in protein folding, as seen with the CFTR protein in cystic fibrosis, would result in abnormal protein functioning. Protein concentration may be normal or low due to more rapid degradation of the abnormal protein.

(Choices D and E) Splicing mutations can result in inappropriate removal of exons or persistence of introns; this



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(Choice C) A defect in protein folding, as seen with the CFTR protein in cystic fibrosis, would result in abnormal protein functioning. Protein concentration may be normal or low due to more rapid degradation of the abnormal protein.

(Choices D and E) Splicing mutations can result in inappropriate removal of exons or persistence of introns; this creates aberrant mRNA that is presented for translation and results in production of an abnormal protein. Similarly, a defect in translation results in insufficient or abnormal protein synthesis, which is reflected both in the serum and intracellularly.

Educational objective:

Posttranslational modification of proteins is important for targeting proteins to the correct location. This step is defective in I-cell disease, which is characterized by a lack of mannose residue phosphorylation, resulting in inappropriate trafficking of acid hydrolases to the extracellular space instead of to lysosomes.

Biochemistry	Biochemistry (General Principles)	Lysosomal storage disorder
Subject	System	Topic

Block Time Elapsed: 00:03:13

Item 16 of 40
Question Id: 8328
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:03:13
My Notebook
Flashcards
Feedback
Suspend
End Block

An infant born to a 34-year-old woman has a flat facial profile, prominent epicanthal folds, and a holosystolic murmur heard loudest at the left sternal border. Karyotype analysis is consistent with trisomy 21. Maternal and paternal karyotypes are normal. A restriction fragment length polymorphism (RFLP) analysis is conducted to determine the parental origin of the extra chromosome. DNA samples from the child, mother, and father are obtained and the DNA is fragmented with a restriction enzyme. The fragments are then sorted by size using the Southern blot technique. Labeling is done using a probe that binds to a specific DNA sequence close to the centromere of chromosome 21. RFLP analysis for the child, mother, and father is shown below.

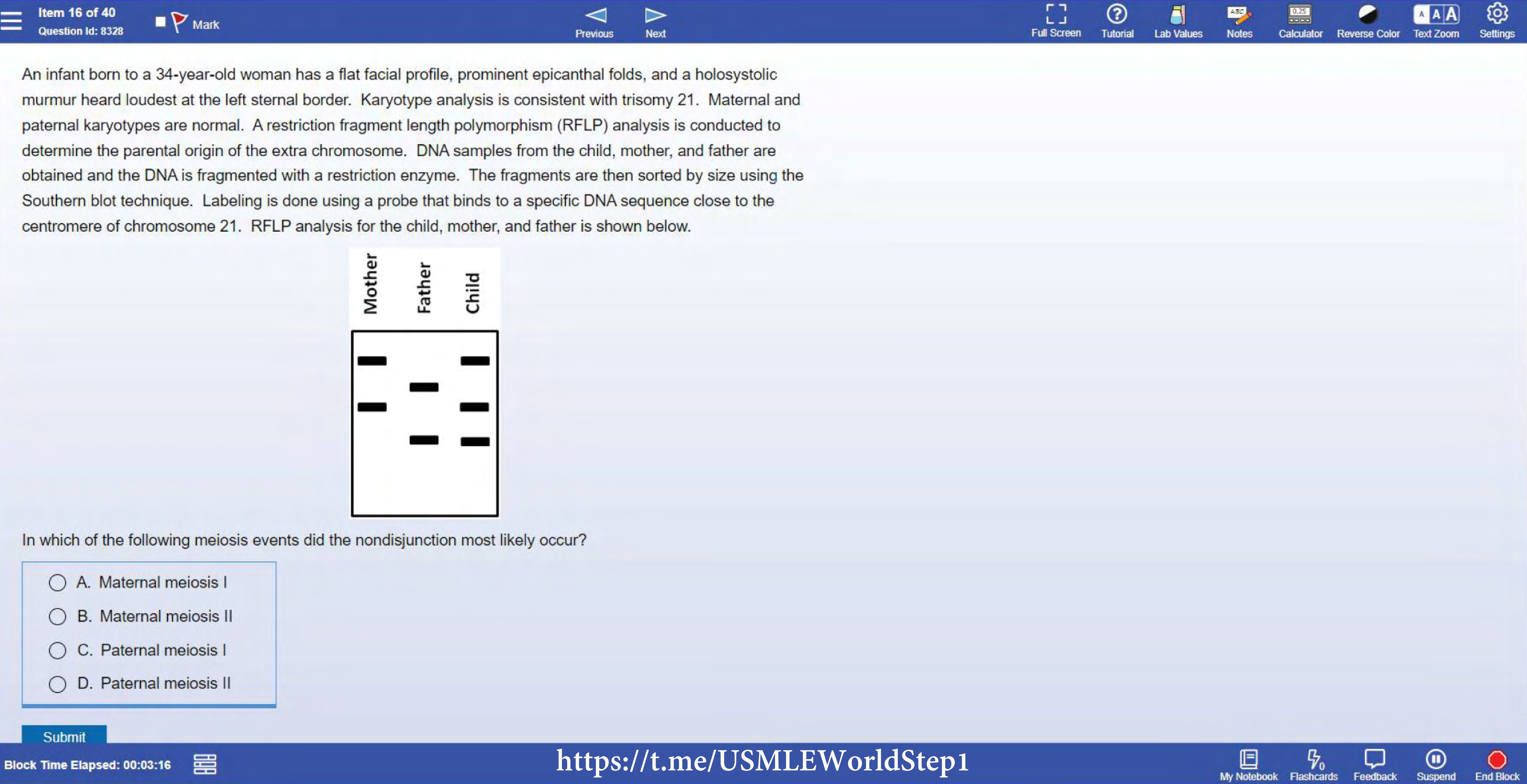
In which of the following meiosis events did the nondisjunction most likely occur?

○ A. Maternal meiosis I

○ B. Maternal meiosis II

○ C. Paternal meiosis I

○ D. Paternal meiosis II


Item 16 of 40
Question Id: 8328
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Mother
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Block Time Elapsed: 00:03:16
My Notebook
Flashcards
Feedback
Suspend
End Block

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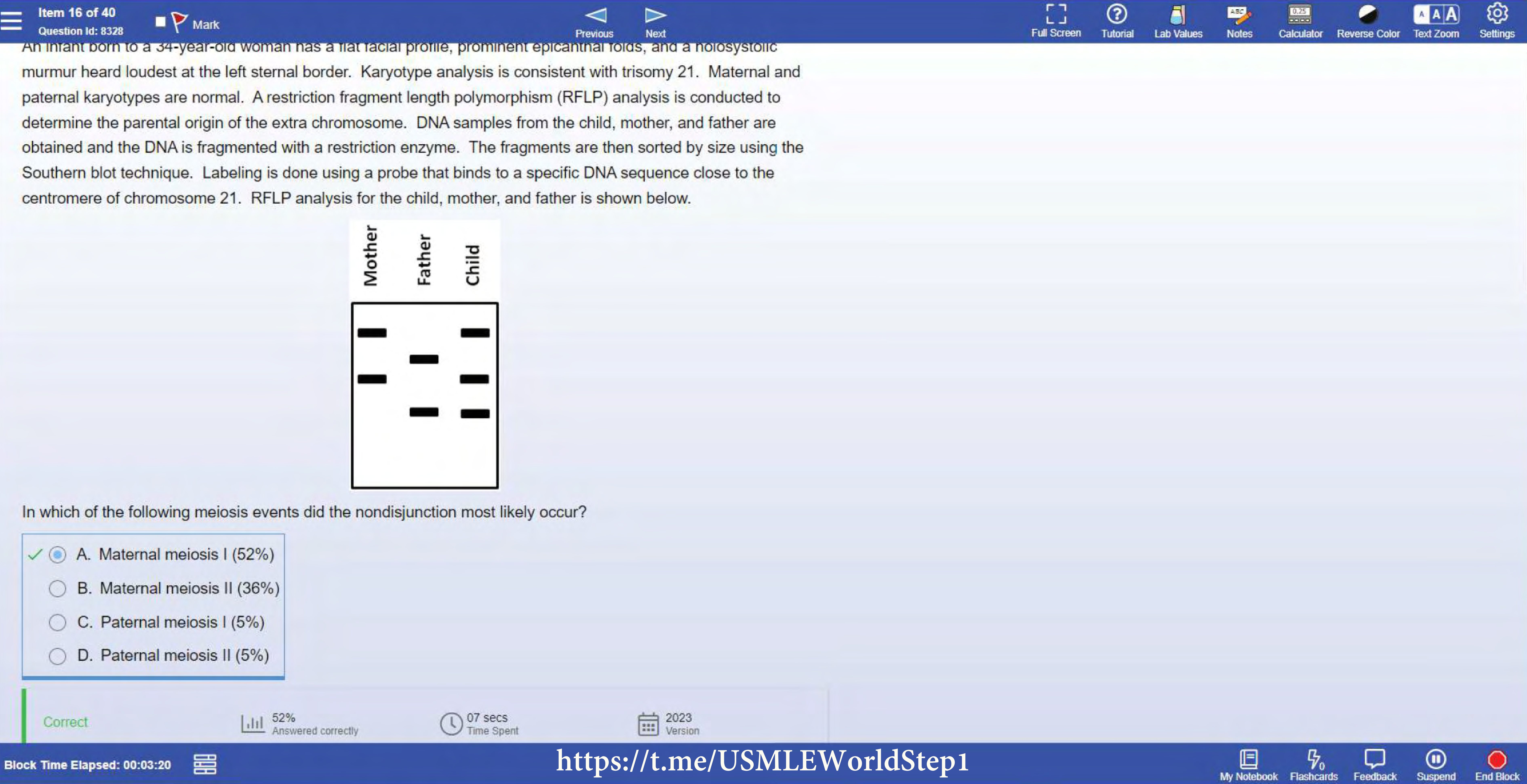
In which of the following meiosis events did the nondisjunction most likely occur?

○ A. Maternal meiosis I
○ B. Maternal meiosis II
○ C. Paternal meiosis I
○ D. Paternal meiosis II


Item 16 of 40
Question Id: 8328
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Mother
Father
Child

In which of the following meiosis events did the nondisjunction most likely occur?

- ✓ ● A. Maternal meiosis I (52%)
- ○ B. Maternal meiosis II (36%)
- ○ C. Paternal meiosis I (5%)
- ○ D. Paternal meiosis II (5%)

Correct

52% Answered correctly

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2023 Version

Block Time Elapsed: 00:03:20

My Notebook
Flashcards
Feedback
Suspend
End Block

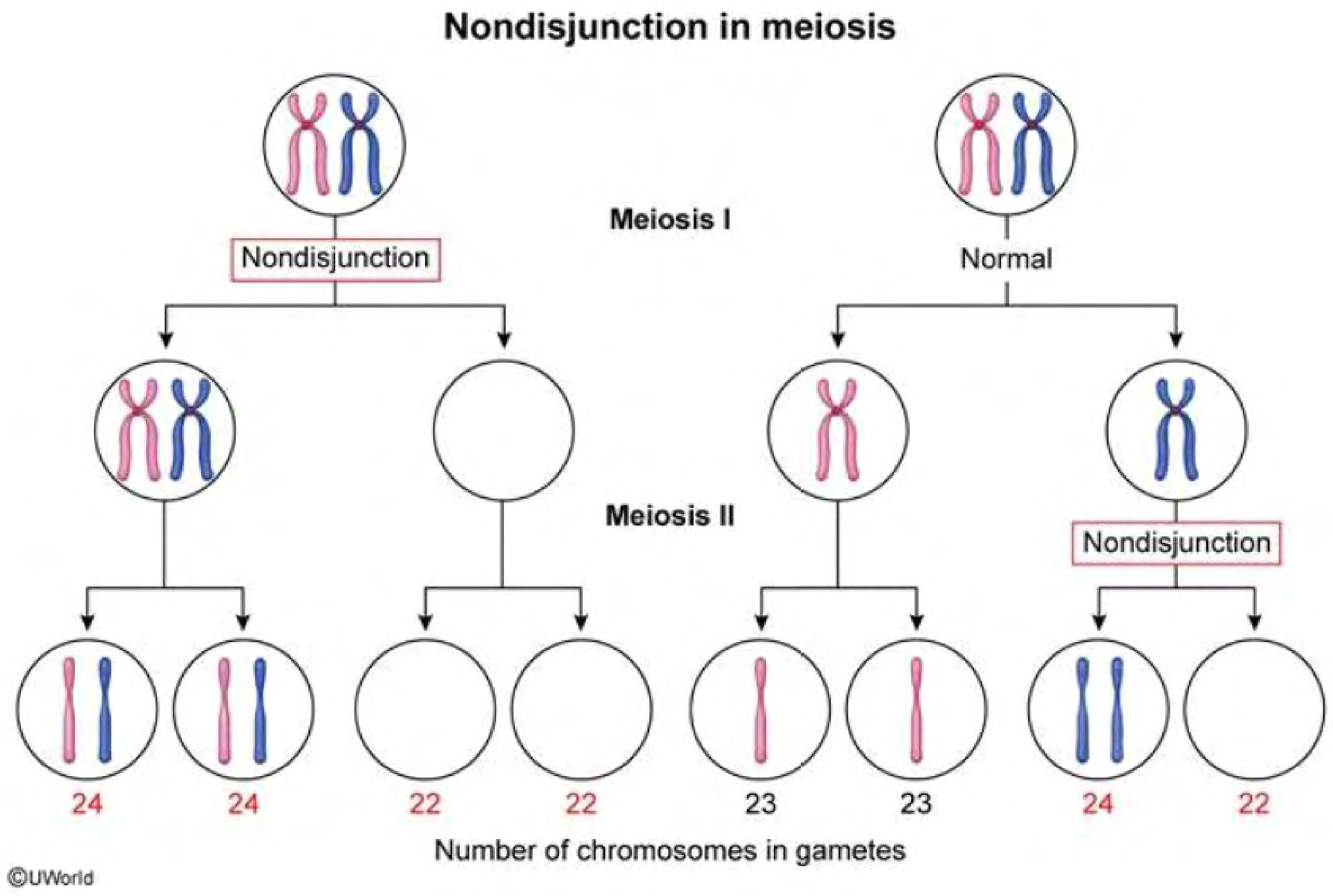
Item 16 of 40
Question Id: 8328

Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Exhibit Display


Nondisjunction in meiosis
Meiosis I
Nondisjunction
Normal
Meiosis II
Nondisjunction
24
24
22
22
23
23
24
22
Number of chromosomes in gametes
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parent
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both o
he inherited both of her homologous chromosomes. Therefore, the problem occurred in the mother during meiosis
I, when homologous chromosomes are separated. In fact, the vast majority of **Down syndrome** cases arise due to

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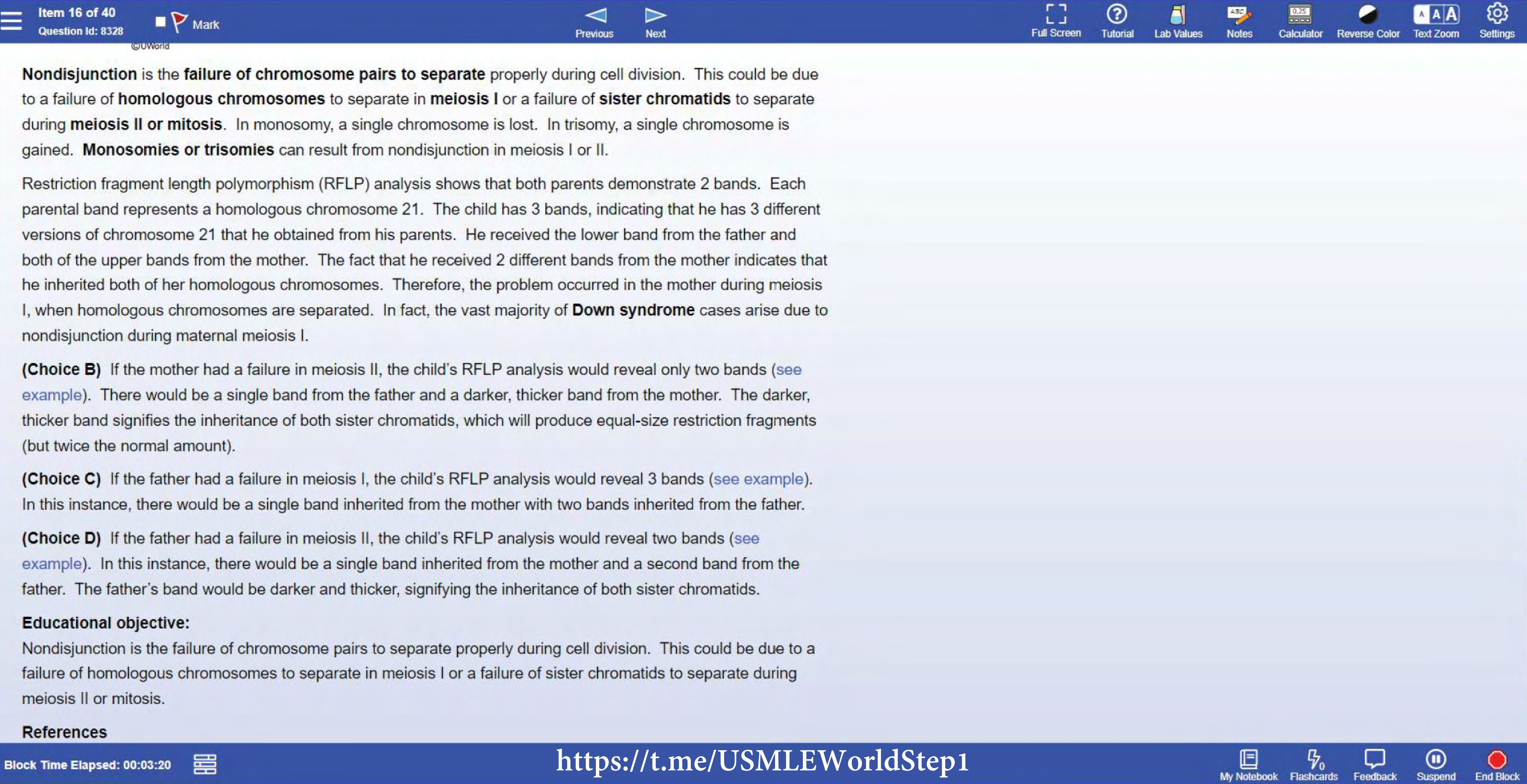

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Nondisjunction is the **failure of chromosome pairs to separate** properly during cell division. This could be due to a failure of **homologous chromosomes** to separate in **meiosis I** or a failure of **sister chromatids** to separate during **meiosis II or mitosis**. In monosomy, a single chromosome is lost. In trisomy, a single chromosome is gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each parental band represents a homologous chromosome 21. The child has 3 bands, indicating that he has 3 different versions of chromosome 21 that he obtained from his parents. He received the lower band from the father and both of the upper bands from the mother. The fact that he received 2 different bands from the mother indicates that he inherited both of her homologous chromosomes. Therefore, the problem occurred in the mother during meiosis I, when homologous chromosomes are separated. In fact, the vast majority of **Down syndrome** cases arise due to nondisjunction during maternal meiosis I.

(Choice B) If the mother had a failure in meiosis II, the child's RFLP analysis would reveal only two bands (see example). There would be a single band from the father and a darker, thicker band from the mother. The darker, thicker band signifies the inheritance of both sister chromatids, which will produce equal-size restriction fragments (but twice the normal amount).

(Choice C) If the father had a failure in meiosis I, the child's RFLP analysis would reveal 3 bands (see example). In this instance, there would be a single band inherited from the mother with two bands inherited from the father.

(Choice D) If the father had a failure in meiosis II, the child's RFLP analysis would reveal two bands (see example). In this instance, there would be a single band inherited from the mother and a second band from the father. The father's band would be darker and thicker, signifying the inheritance of both sister chromatids.

Educational objective:

Nondisjunction is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of homologous chromosomes to separate in meiosis I or a failure of sister chromatids to separate during meiosis II or mitosis.

References

Nondisjunction is the **failure of chromosome pairs to separate** properly during cell division. This could be due

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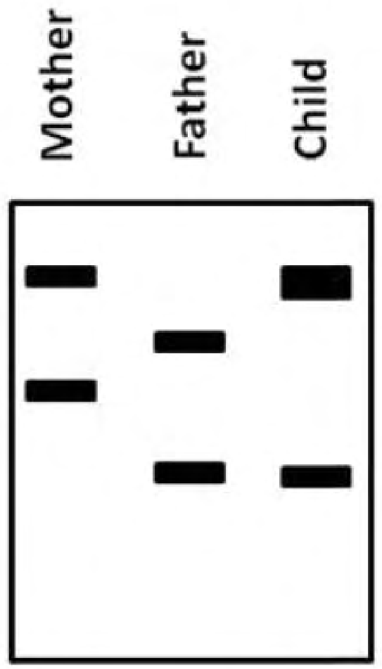

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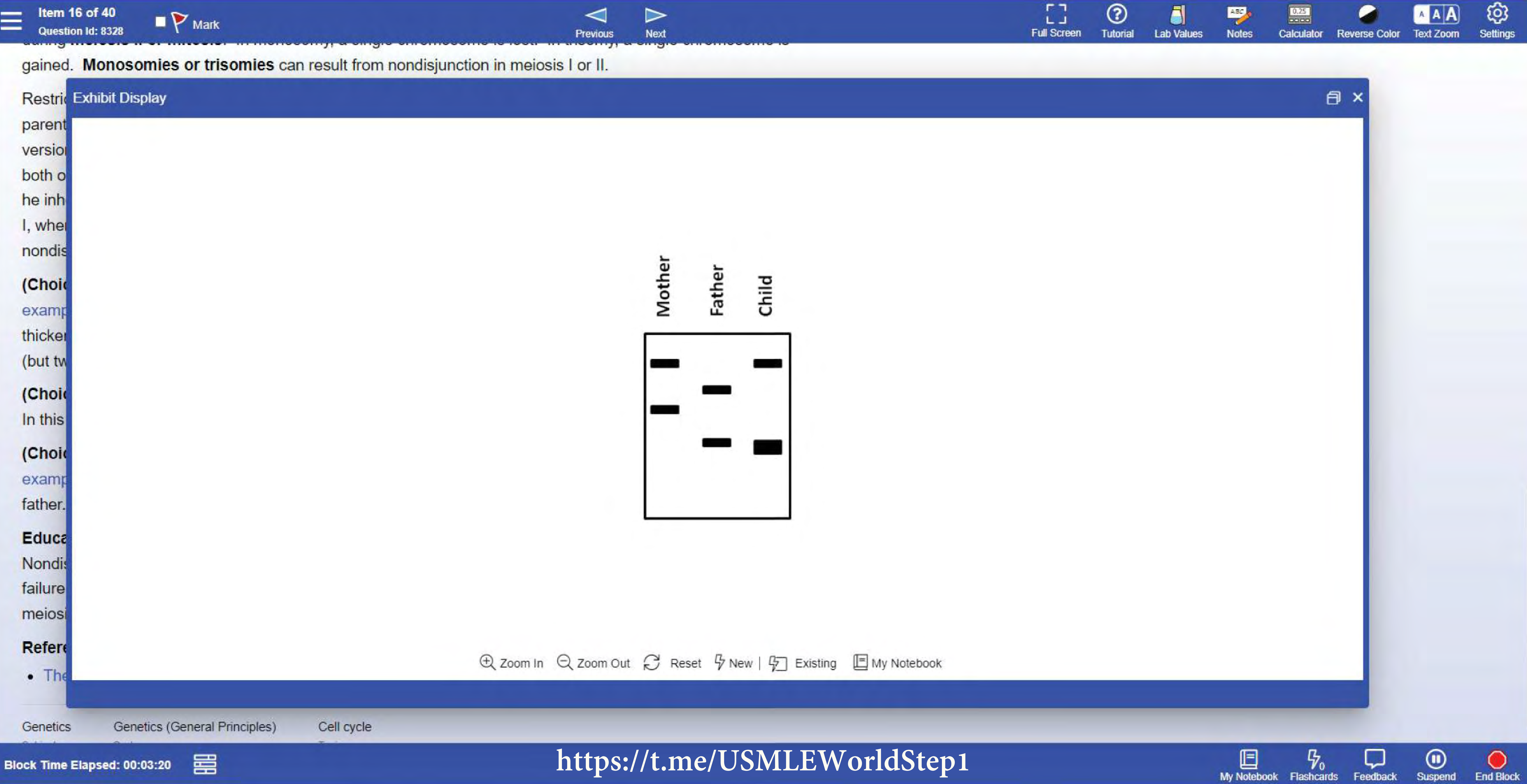
Item 16 of 40
Question Id: 8328
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gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

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Genetics Genetics (General Principles) Cell cycle

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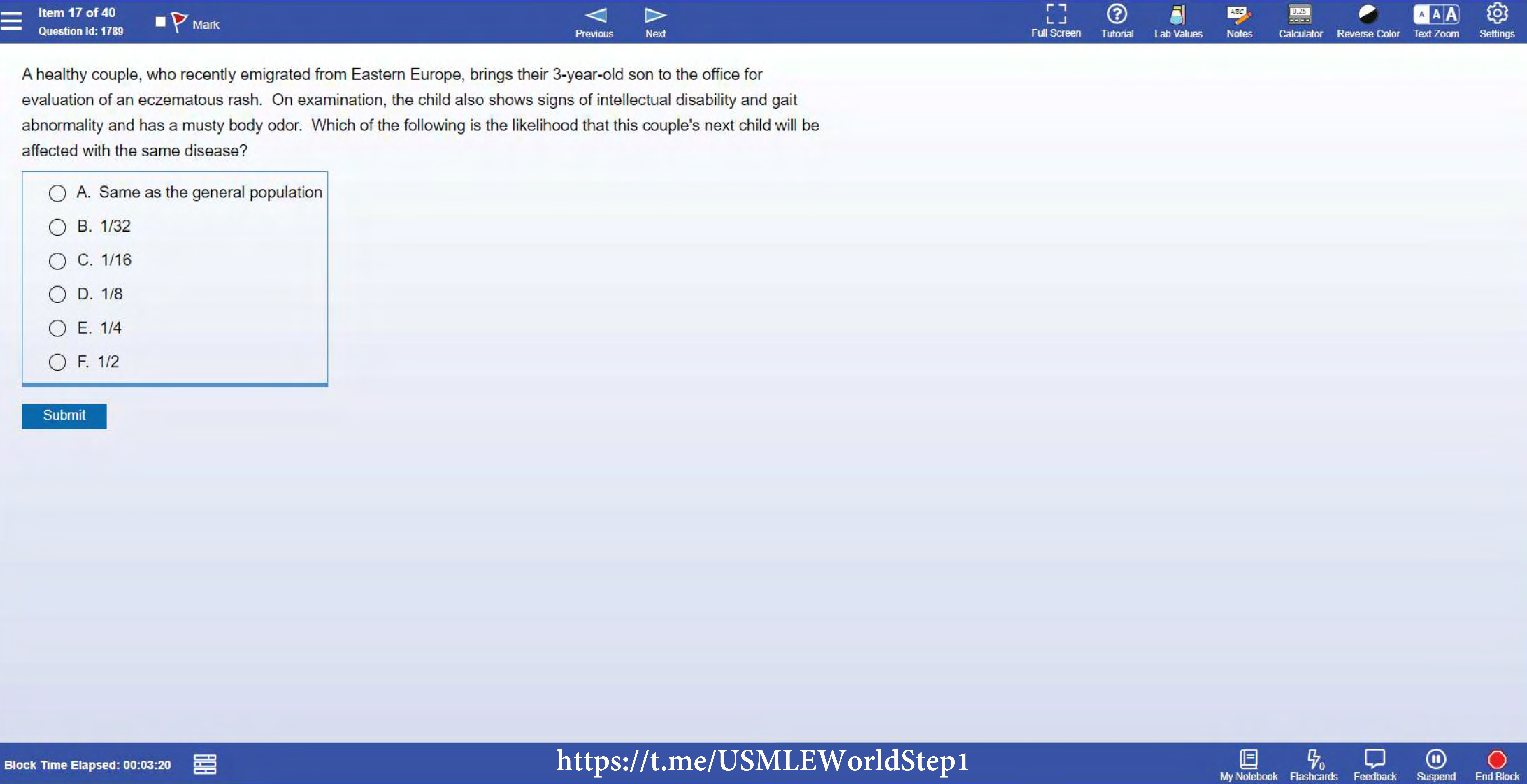
Item 17 of 40
Question Id: 1789
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Full Screen
Tutorial
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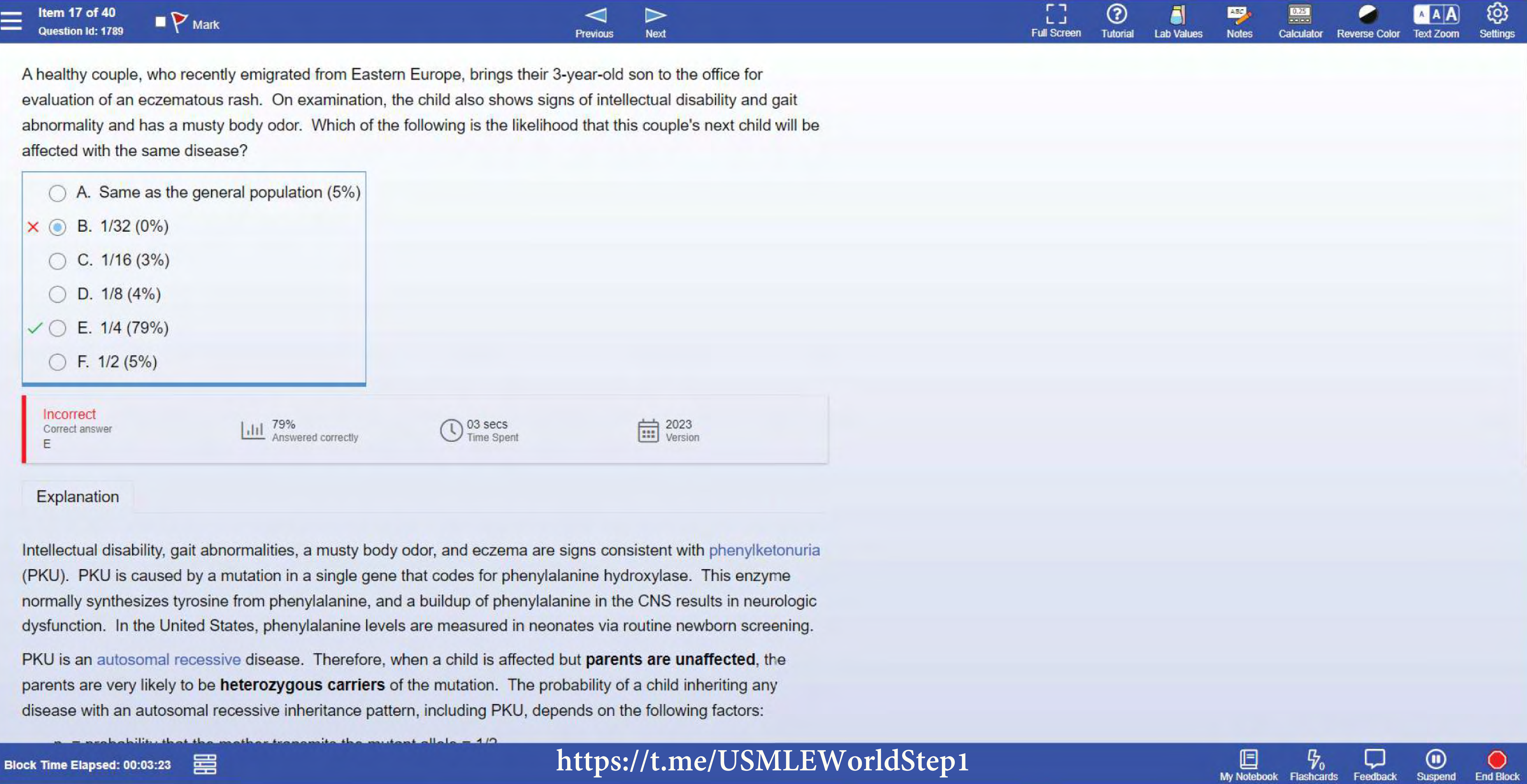
A healthy couple, who recently emigrated from Eastern Europe, brings their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. Which of the following is the likelihood that this couple's next child will be affected with the same disease?

○ A. Same as the general population
○ B. 1/32
○ C. 1/16
○ D. 1/8
○ E. 1/4
○ F. 1/2


Item 17 of 40
Question Id: 1789
Mark
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A healthy couple, who recently emigrated from Eastern Europe, brings their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. Which of the following is the likelihood that this couple's next child will be affected with the same disease?

- ○ A. Same as the general population (5%)
- ✗ ● B. 1/32 (0%)
- ○ C. 1/16 (3%)
- ○ D. 1/8 (4%)
- ✓ ○ E. 1/4 (79%)
- ○ F. 1/2 (5%)

Incorrect
Correct answer
E

79%
Answered correctly

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Explanation

Intellectual disability, gait abnormalities, a musty body odor, and eczema are signs consistent with phenylketonuria (PKU). PKU is caused by a mutation in a single gene that codes for phenylalanine hydroxylase. This enzyme normally synthesizes tyrosine from phenylalanine, and a buildup of phenylalanine in the CNS results in neurologic dysfunction. In the United States, phenylalanine levels are measured in neonates via routine newborn screening.

PKU is an autosomal recessive disease. Therefore, when a child is affected but **parents are unaffected**, the parents are very likely to be **heterozygous carriers** of the mutation. The probability of a child inheriting any disease with an autosomal recessive inheritance pattern, including PKU, depends on the following factors:

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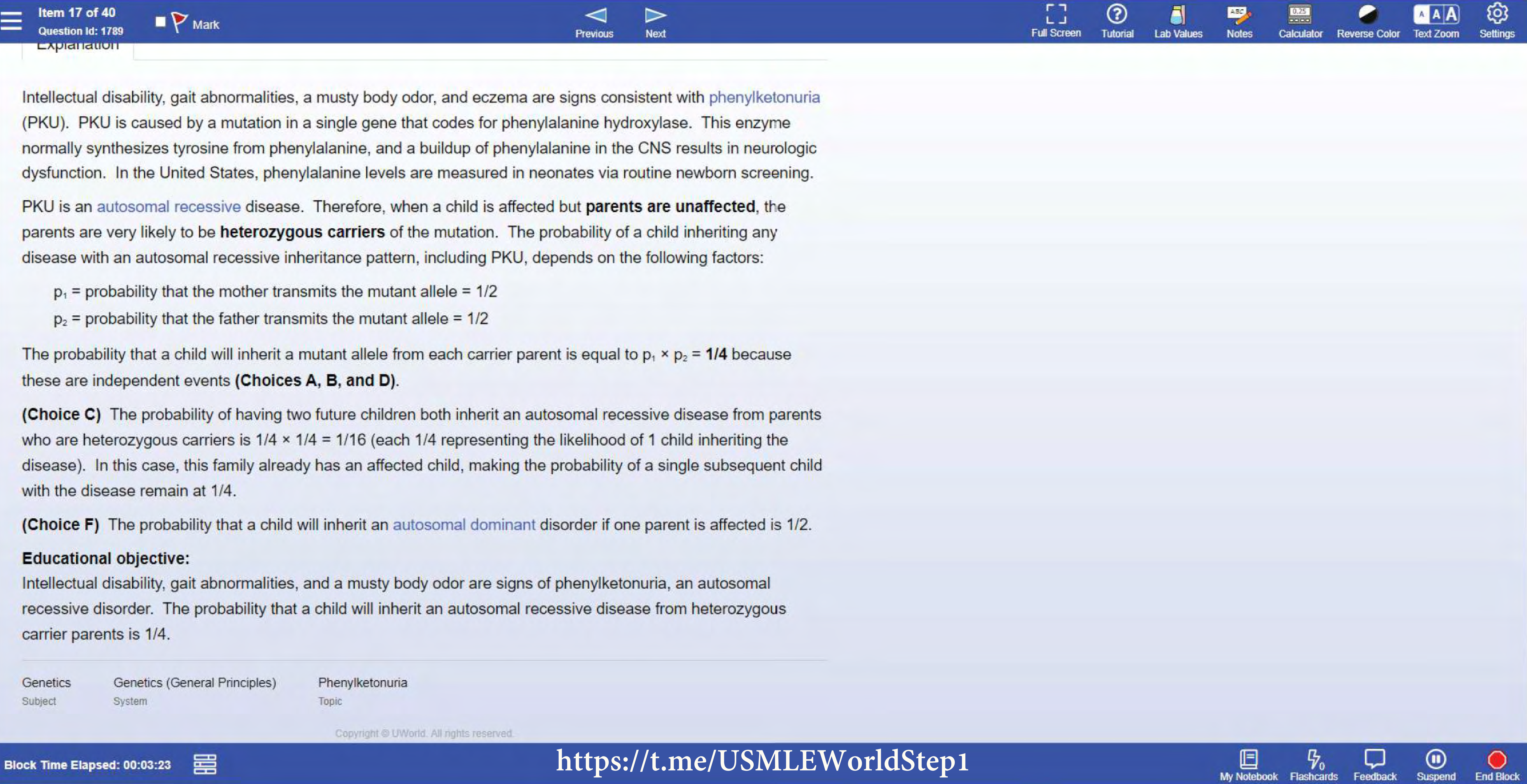
Item 17 of 40
Question Id: 1789
Mark
Previous
Next
Full Screen
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Notes
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Text Zoom
Settings
Explanation

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p_1 = probability that the mother transmits the mutant allele = 1/2
p_2 = probability that the father transmits the mutant allele = 1/2

The probability that a child will inherit a mutant allele from each carrier parent is equal to $p_1 \times p_2$ = **1/4** because these are independent events **(Choices A, B, and D)**.

(Choice C) The probability of having two future children both inherit an autosomal recessive disease from parents who are heterozygous carriers is 1/4 × 1/4 = 1/16 (each 1/4 representing the likelihood of 1 child inheriting the disease). In this case, this family already has an affected child, making the probability of a single subsequent child with the disease remain at 1/4.

(Choice F) The probability that a child will inherit an autosomal dominant disorder if one parent is affected is 1/2.

Educational objective:
Intellectual disability, gait abnormalities, and a musty body odor are signs of phenylketonuria, an autosomal recessive disorder. The probability that a child will inherit an autosomal recessive disease from heterozygous carrier parents is 1/4.

Genetics	Genetics (General Principles)	Phenylketonuria
Subject	System	Topic

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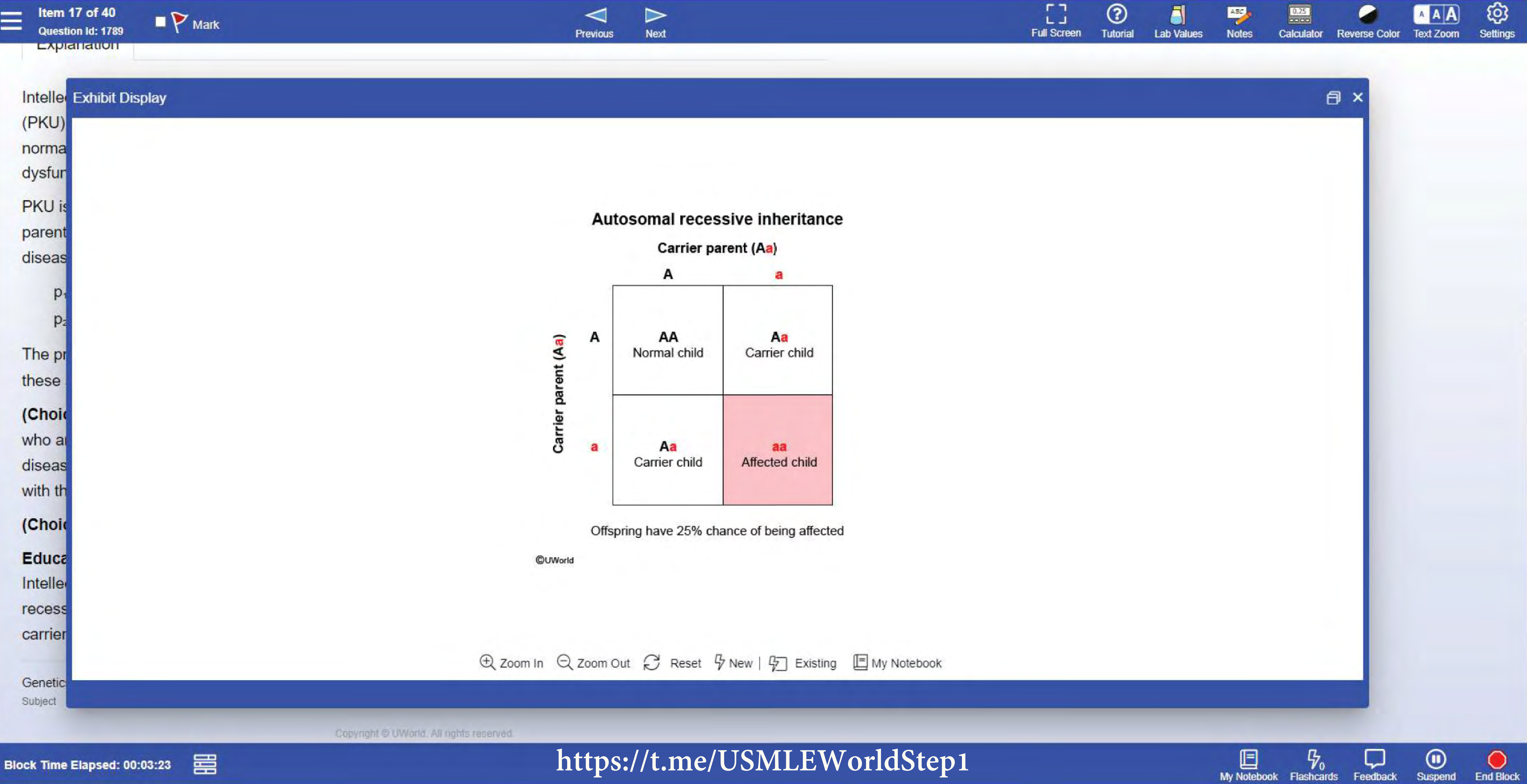
Item 17 of 40
Question Id: 1789
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Autosomal recessive inheritance

Carrier parent (Aa)

Carrier parent (Aa)	**A**	**a**
A	**AA** Normal child	**Aa** Carrier child
a	**Aa** Carrier child	**aa** Affected child

Offspring have 25% chance of being affected

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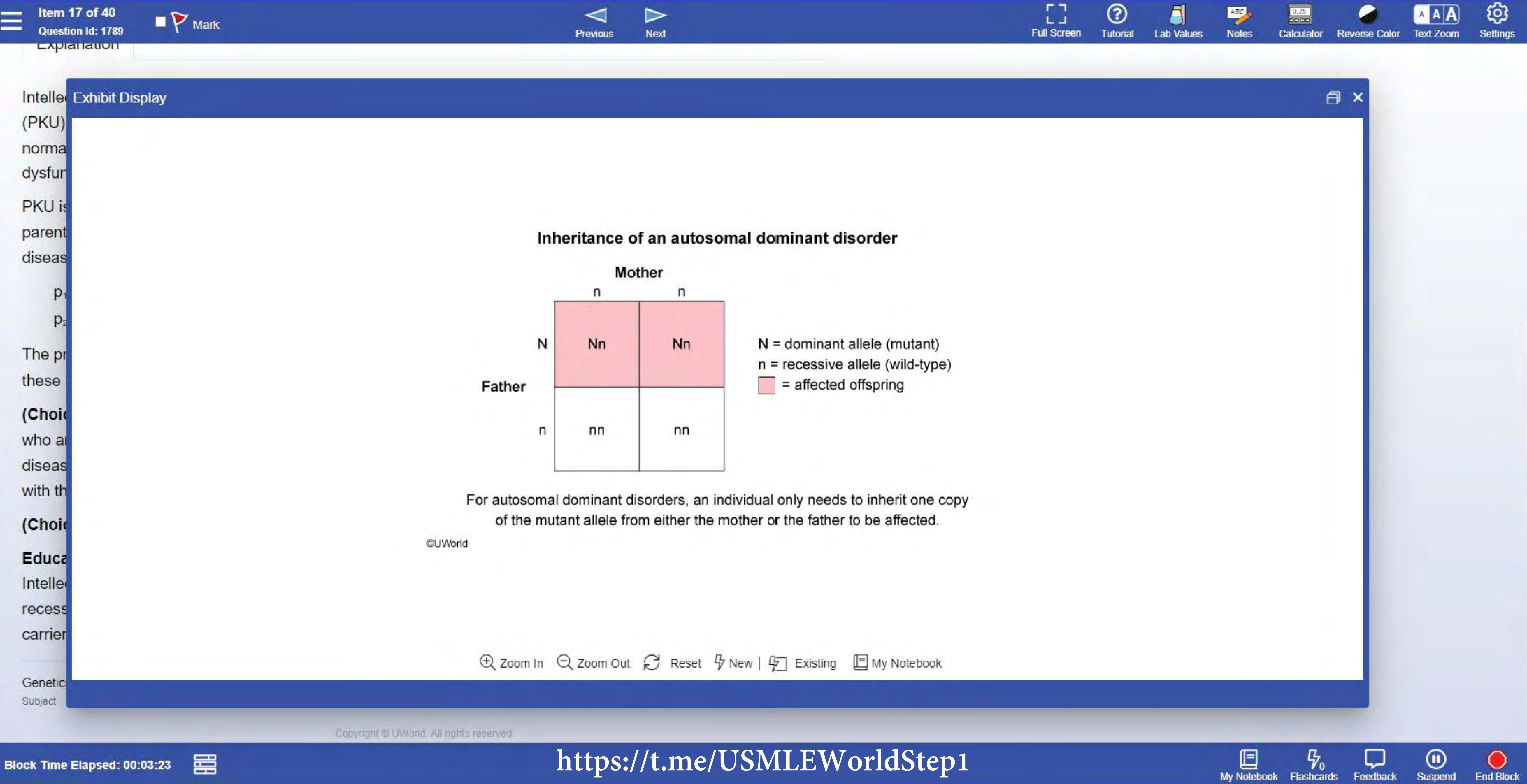
Item 17 of 40
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Inheritance of an autosomal dominant disorder

Mother

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Father	N	Nn	Nn
	n	nn	nn

N = dominant allele (mutant)
n = recessive allele (wild-type)
🟥 = affected offspring

For autosomal dominant disorders, an individual only needs to inherit one copy of the mutant allele from either the mother or the father to be affected.

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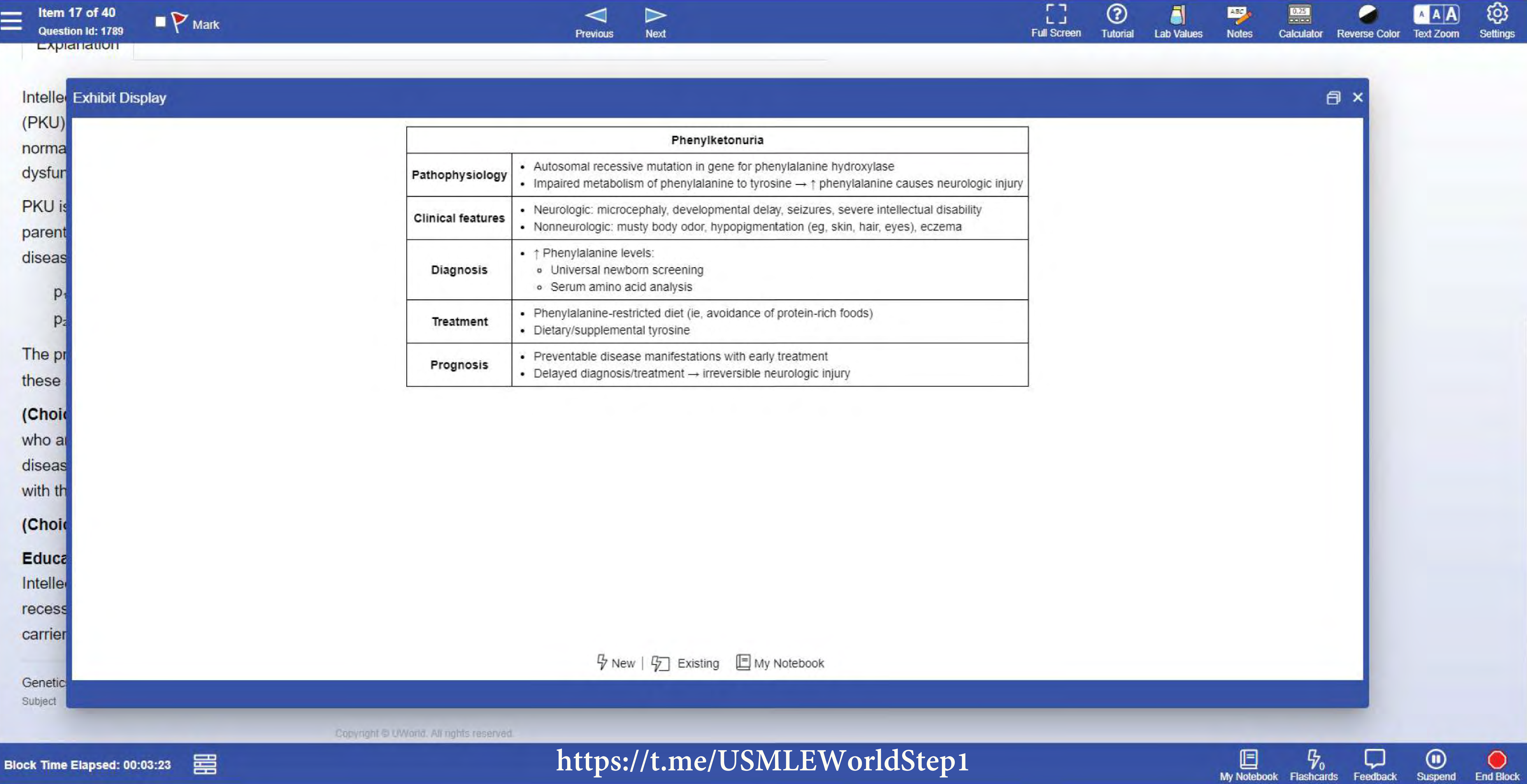
Item 17 of 40
Question Id: 1789
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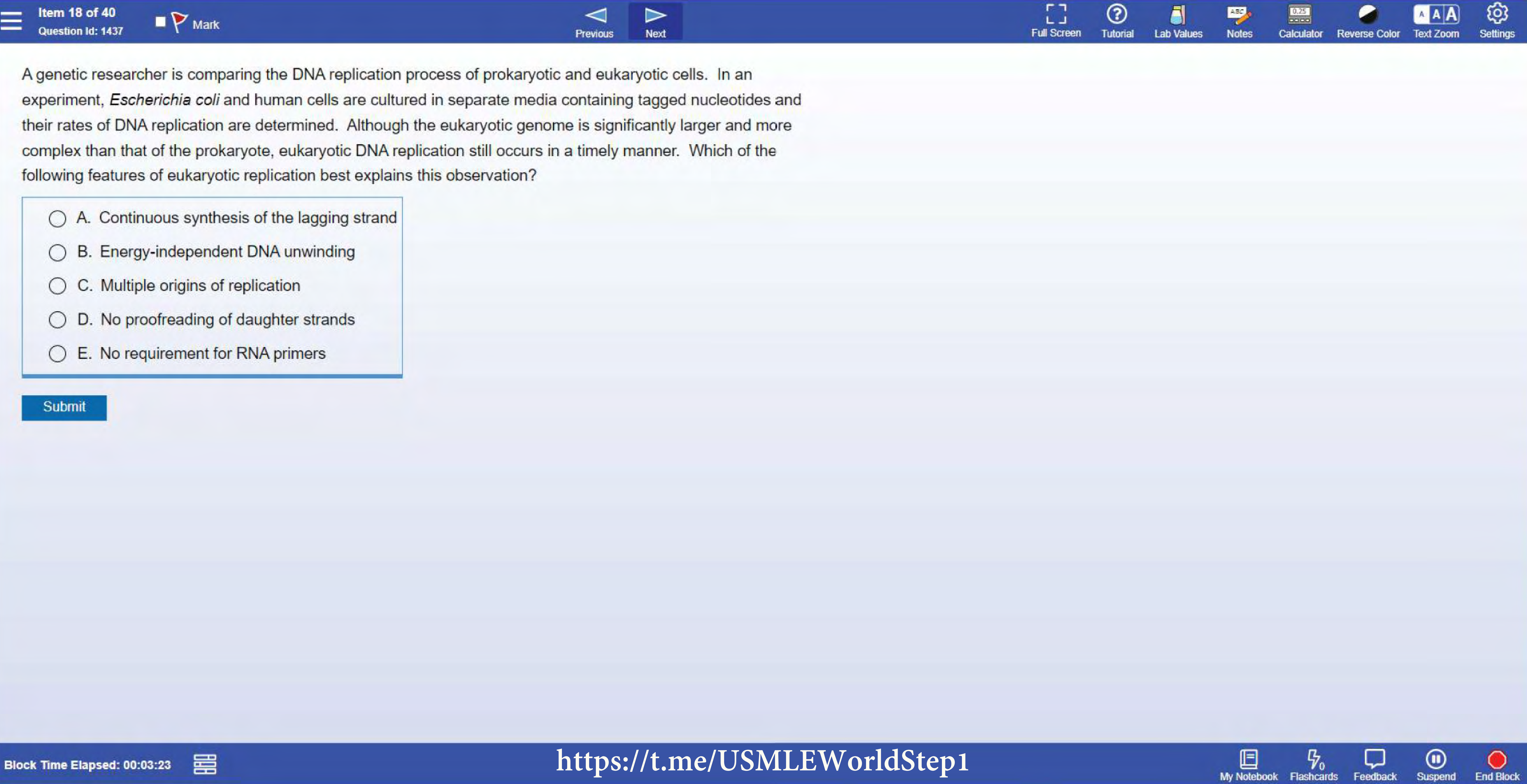
My Notebook
Flashcards
Feedback
Suspend
End Block

Phenylketonuria	
Pathophysiology	• Autosomal recessive mutation in gene for phenylalanine hydroxylase • Impaired metabolism of phenylalanine to tyrosine → ↑ phenylalanine causes neurologic injury
Clinical features	• Neurologic: microcephaly, developmental delay, seizures, severe intellectual disability • Nonneurologic: musty body odor, hypopigmentation (eg, skin, hair, eyes), eczema
Diagnosis	• ↑ Phenylalanine levels: ∘ Universal newborn screening ∘ Serum amino acid analysis
Treatment	• Phenylalanine-restricted diet (ie, avoidance of protein-rich foods) • Dietary/supplemental tyrosine
Prognosis	• Preventable disease manifestations with early treatment • Delayed diagnosis/treatment → irreversible neurologic injury


Item 18 of 40
Question Id: 1437
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

○ A. Continuous synthesis of the lagging strand
○ B. Energy-independent DNA unwinding
○ C. Multiple origins of replication
○ D. No proofreading of daughter strands
○ E. No requirement for RNA primers

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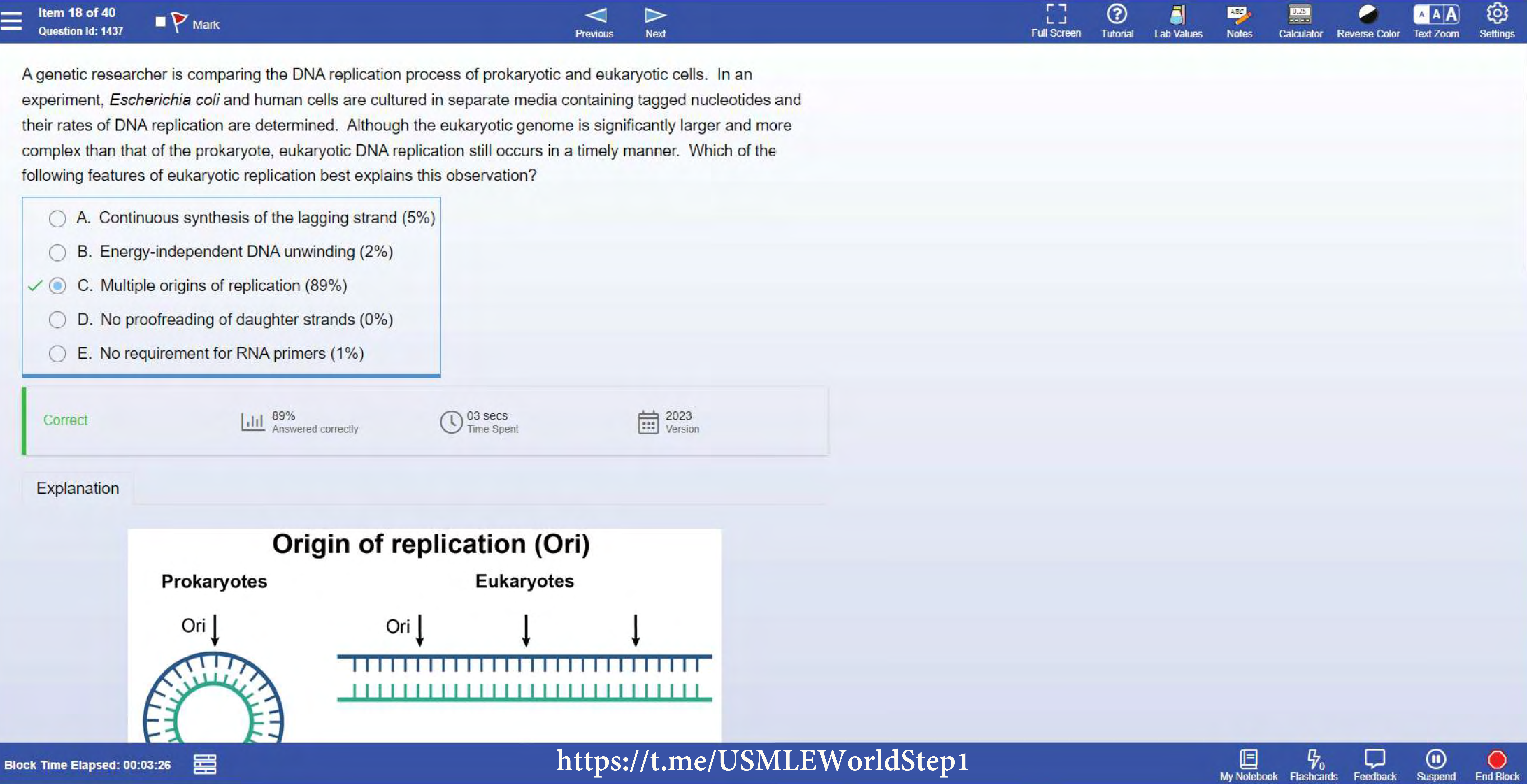
Item 18 of 40
Question Id: 1437
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

- ○ A. Continuous synthesis of the lagging strand (5%)
- ○ B. Energy-independent DNA unwinding (2%)
- ✓ ● C. Multiple origins of replication (89%)
- ○ D. No proofreading of daughter strands (0%)
- ○ E. No requirement for RNA primers (1%)

Correct

89% Answered correctly

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Explanation

Origin of replication (Ori)
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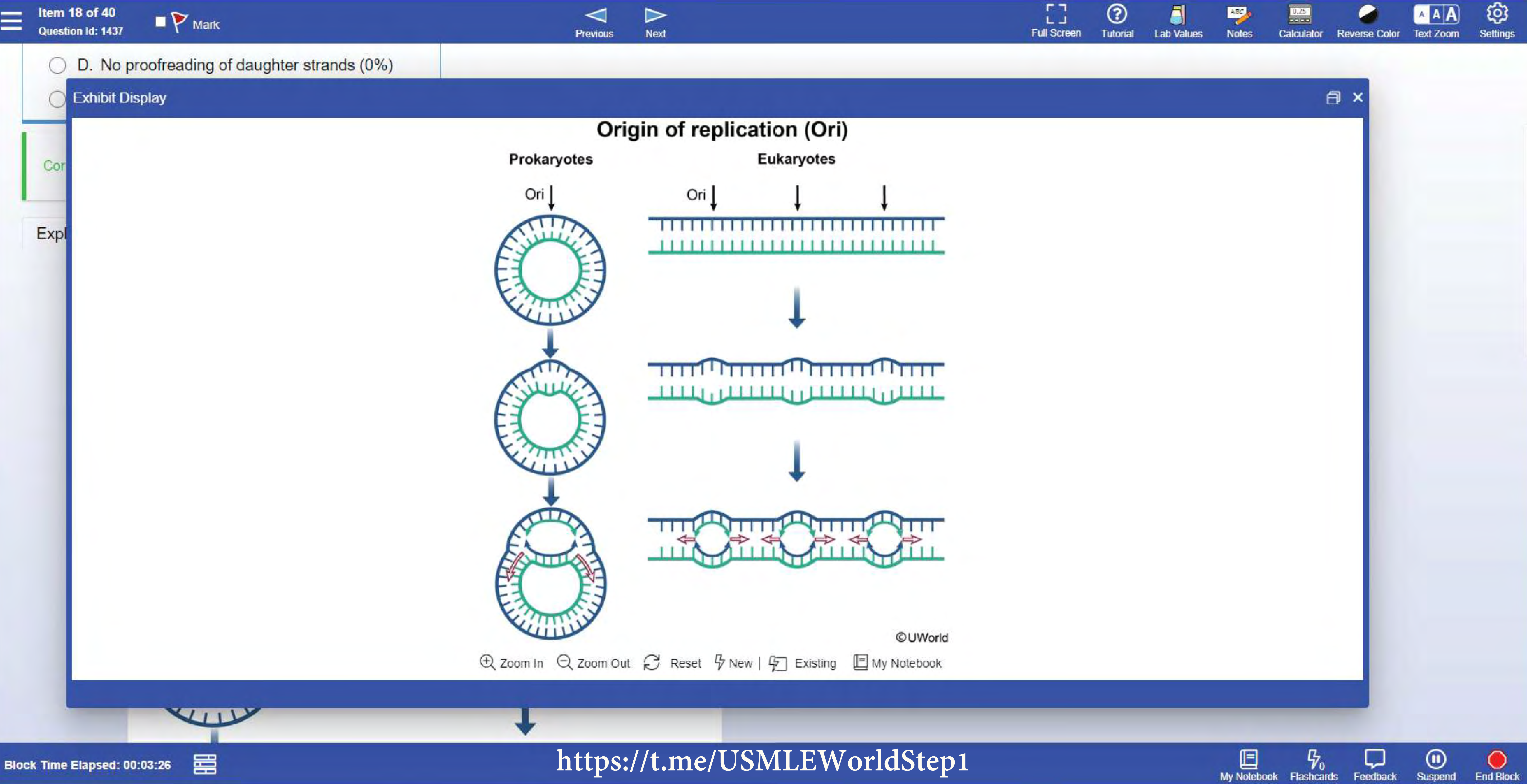
Item 18 of 40
Question Id: 1437
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

○ D. No proofreading of daughter strands (0%)

Exhibit Display

Origin of replication (Ori)

Prokaryotes
Eukaryotes
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Block Time Elapsed: 00:03:26
My Notebook
Flashcards
Feedback
Suspend
End Block

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The key steps of DNA replication are similar in eukaryotes and prokaryotes (eg, *Escherichia coli*) and are as follows:

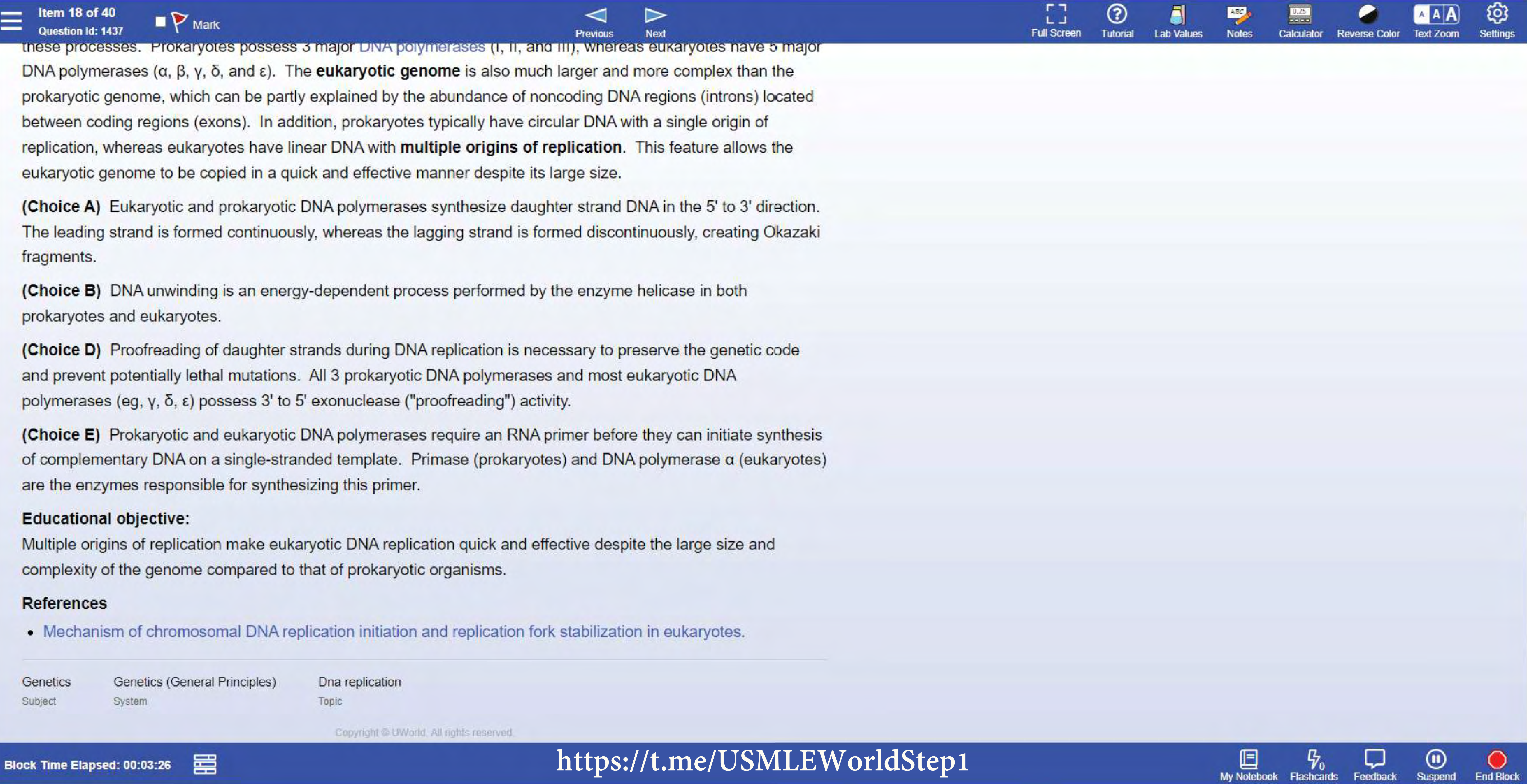
1. Unwinding of double-stranded DNA by helicase to produce single-stranded DNA
2. Formation of a replication fork
3. Synthesis of RNA primers by the enzyme primase
4. Synthesis and concurrent proofreading of daughter DNA strands by DNA polymerases
5. Removal and replacement of RNA primers with DNA
6. Ligation of Okazaki fragments on lagging strands by the enzyme ligase

Despite the similarities of prokaryotic and eukaryotic DNA replication, there are important differences between these processes. Prokaryotes possess 3 major DNA polymerases (I, II, and III), whereas eukaryotes have 5 major DNA polymerases (α, β, γ, δ, and ε). The **eukaryotic genome** is also much larger and more complex than the prokaryotic genome, which can be partly explained by the abundance of noncoding DNA regions (introns) located between coding regions (exons). In addition, prokaryotes typically have circular DNA with a single origin of replication, whereas eukaryotes have linear DNA with **multiple origins of replication**. This feature allows the eukaryotic genome to be copied in a quick and effective manner despite its large size.

(Choice A) Eukaryotic and prokaryotic DNA polymerases synthesize daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice B) DNA unwinding is an energy-dependent process performed by the enzyme helicase in both prokaryotes and eukaryotes.

(Choice D) Proofreading of daughter strands during DNA replication is necessary to preserve the genetic code and prevent potentially lethal mutations. All 3 prokaryotic DNA polymerases and most eukaryotic DNA polymerases (eg, γ, δ, ε) possess 3' to 5' exonuclease ("proofreading") activity.



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(Choice B) DNA unwinding is an energy-dependent process performed by the enzyme helicase in both prokaryotes and eukaryotes.

(Choice D) Proofreading of daughter strands during DNA replication is necessary to preserve the genetic code and prevent potentially lethal mutations. All 3 prokaryotic DNA polymerases and most eukaryotic DNA polymerases (eg, γ, δ, ε) possess 3' to 5' exonuclease ("proofreading") activity.

(Choice E) Prokaryotic and eukaryotic DNA polymerases require an RNA primer before they can initiate synthesis of complementary DNA on a single-stranded template. Primase (prokaryotes) and DNA polymerase α (eukaryotes) are the enzymes responsible for synthesizing this primer.

Educational objective:

Multiple origins of replication make eukaryotic DNA replication quick and effective despite the large size and complexity of the genome compared to that of prokaryotic organisms.

References

- Mechanism of chromosomal DNA replication initiation and replication fork stabilization in eukaryotes.

Genetics	Genetics (General Principles)	Dna replication
Subject	System	Topic

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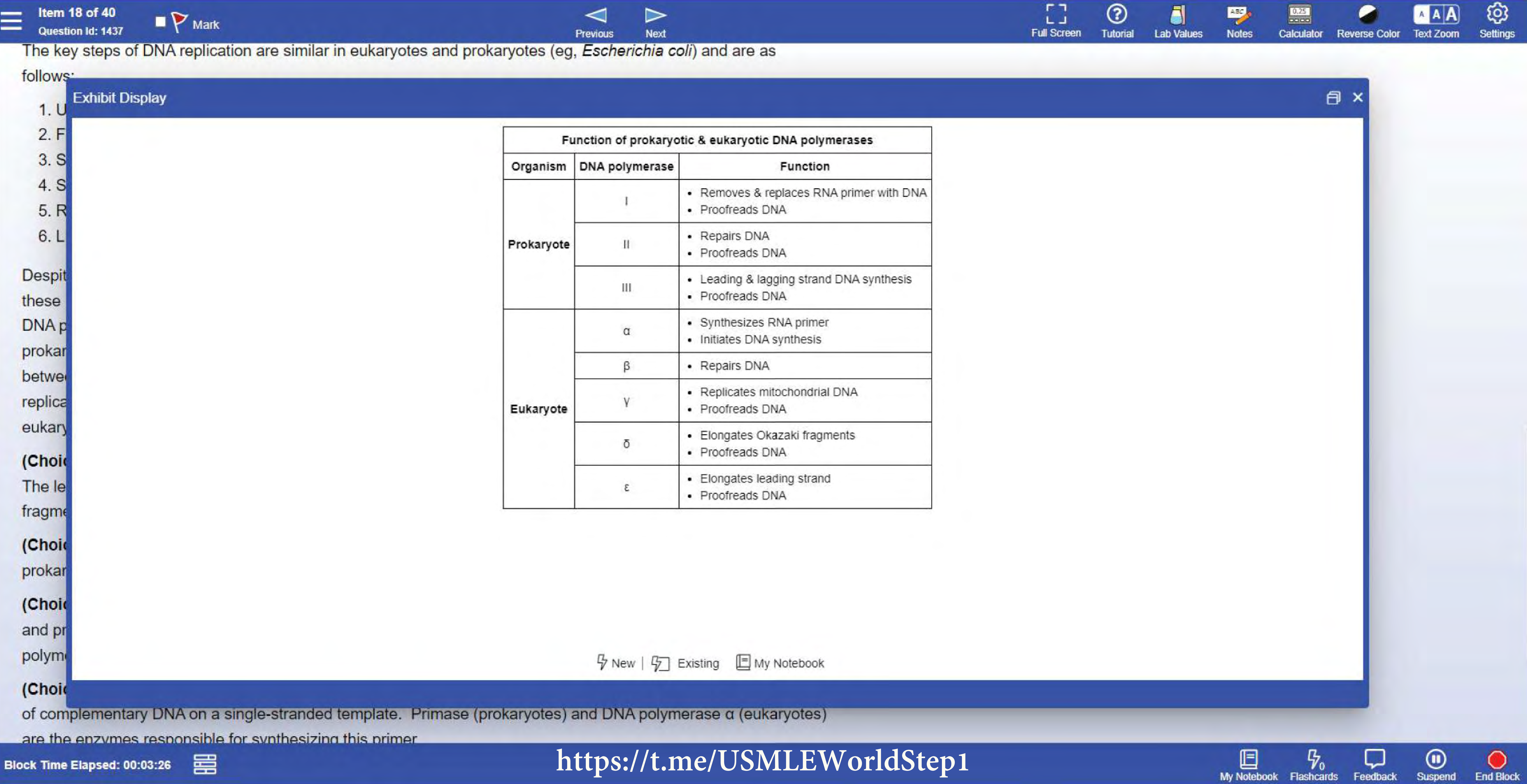
Item 18 of 40
Question Id: 1437
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
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Calculator
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The key steps of DNA replication are similar in eukaryotes and prokaryotes (eg, *Escherichia coli*) and are as follows:

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of complementary DNA on a single-stranded template. Primase (prokaryotes) and DNA polymerase α (eukaryotes) are the enzymes responsible for synthesizing this primer.

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Function of prokaryotic & eukaryotic DNA polymerases

Organism	DNA polymerase	Function
Prokaryote	I	• Removes & replaces RNA primer with DNA • Proofreads DNA
	II	• Repairs DNA • Proofreads DNA
	III	• Leading & lagging strand DNA synthesis • Proofreads DNA
Eukaryote	α	• Synthesizes RNA primer • Initiates DNA synthesis
	β	• Repairs DNA
	γ	• Replicates mitochondrial DNA • Proofreads DNA
	δ	• Elongates Okazaki fragments • Proofreads DNA
	ε	• Elongates leading strand • Proofreads DNA

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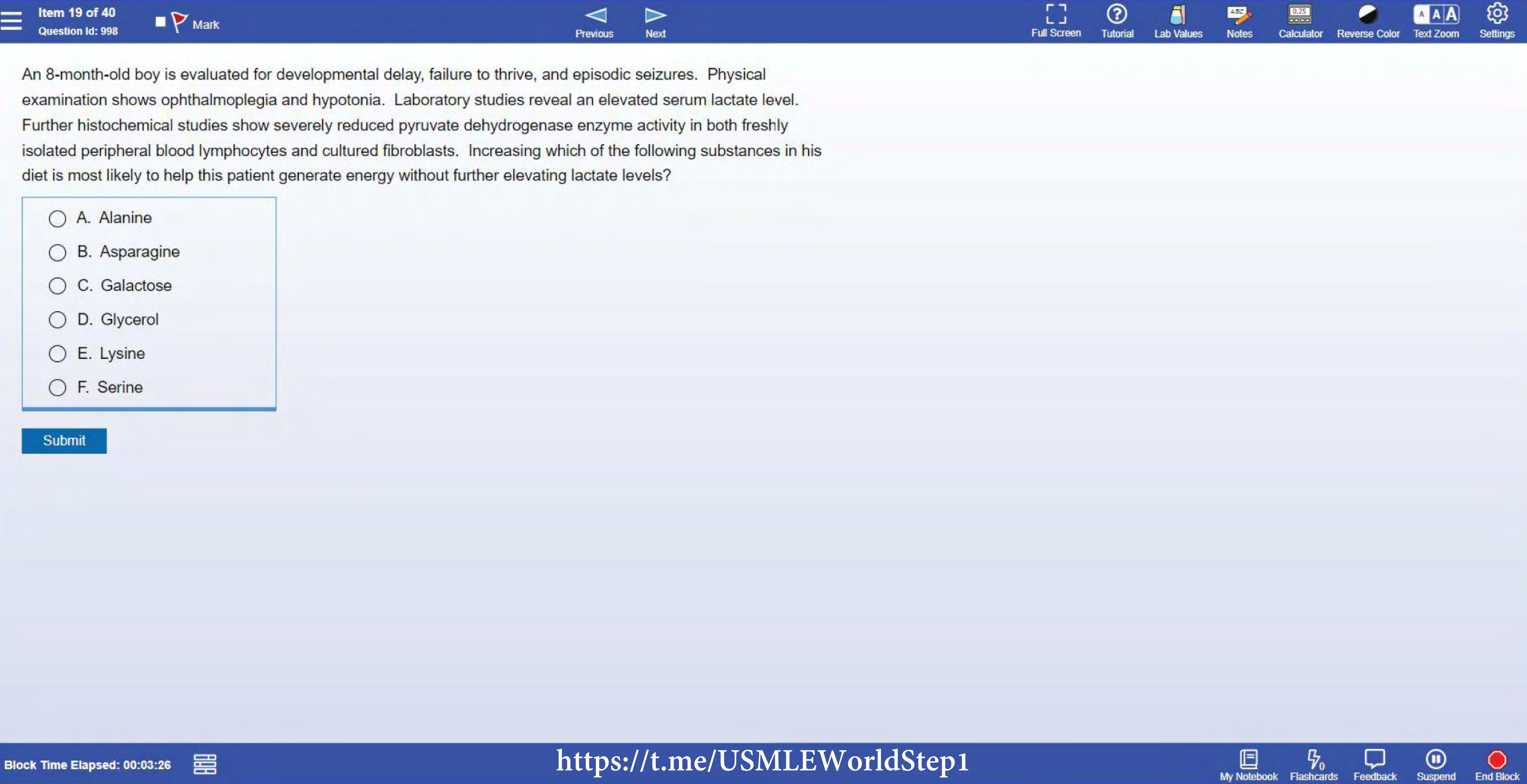
Item 19 of 40
Question Id: 998
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

- ○ A. Alanine
- ○ B. Asparagine
- ○ C. Galactose
- ○ D. Glycerol
- ○ E. Lysine
- ○ F. Serine

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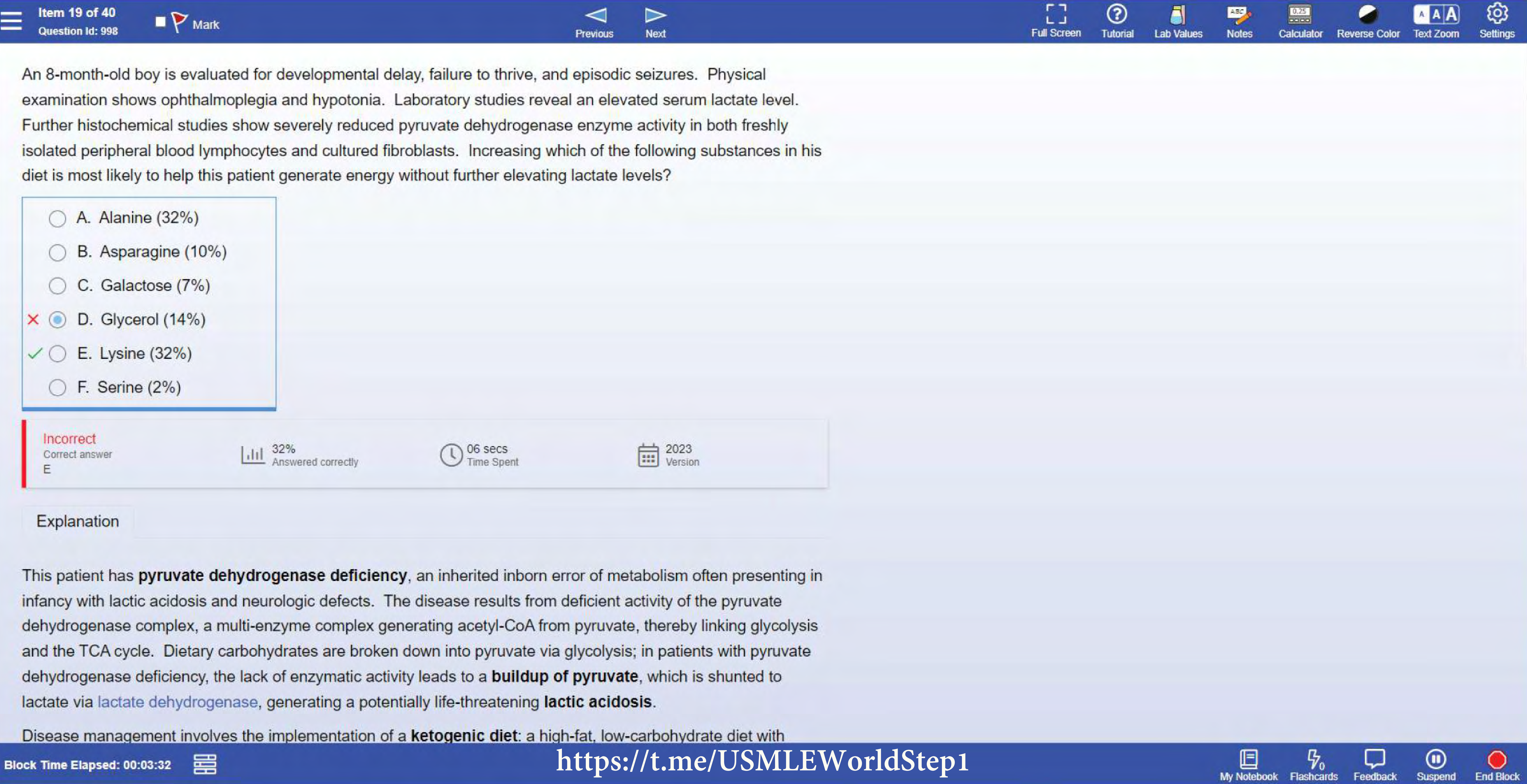

Item 19 of 40
Question Id: 998
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Previous
Next
Full Screen
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An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

- ○ A. Alanine (32%)
- ○ B. Asparagine (10%)
- ○ C. Galactose (7%)
- ✗ ● D. Glycerol (14%)
- ✓ ○ E. Lysine (32%)
- ○ F. Serine (2%)

Incorrect
Correct answer
E

32%
Answered correctly

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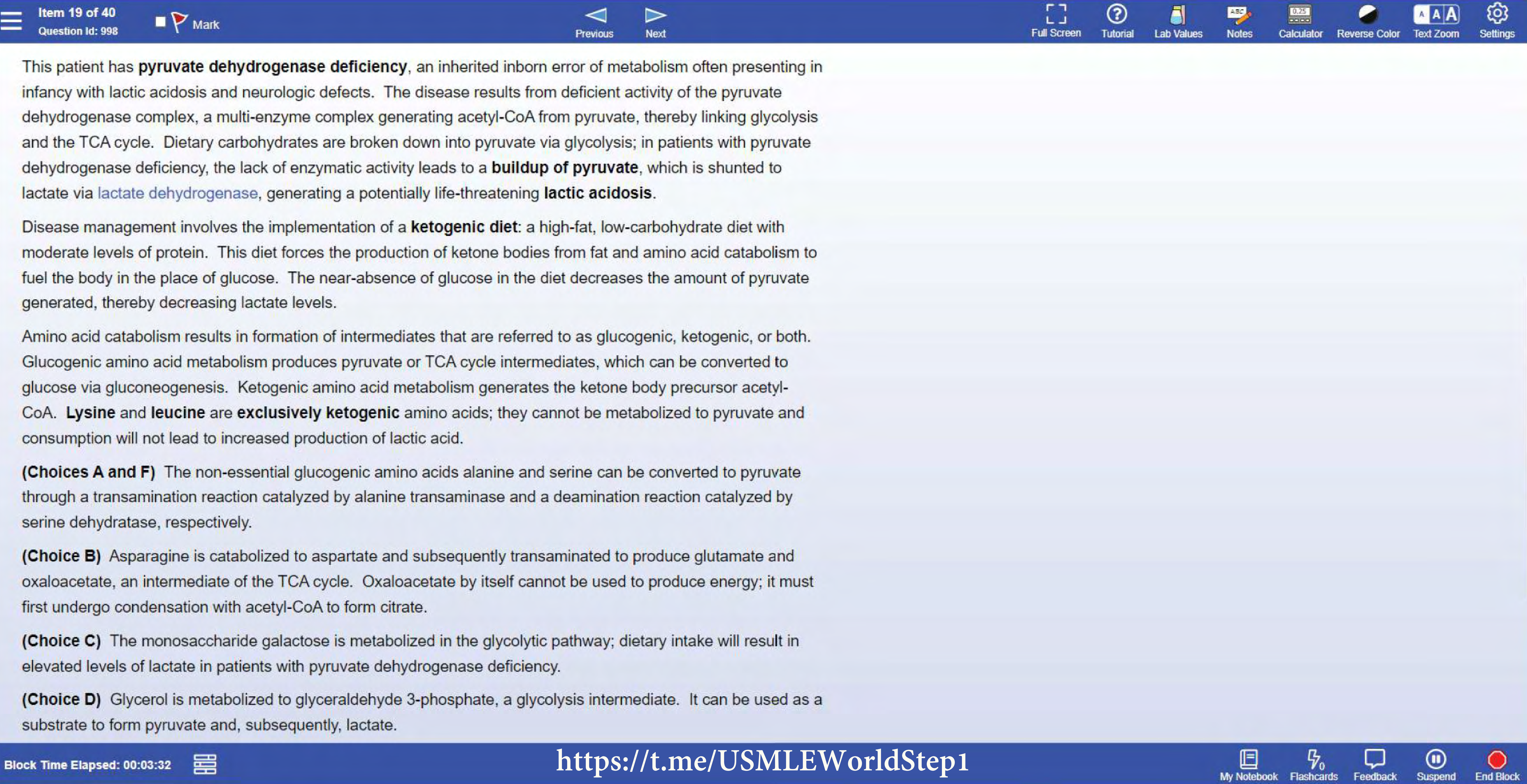
Explanation

This patient has **pyruvate dehydrogenase deficiency**, an inherited inborn error of metabolism often presenting in infancy with lactic acidosis and neurologic defects. The disease results from deficient activity of the pyruvate dehydrogenase complex, a multi-enzyme complex generating acetyl-CoA from pyruvate, thereby linking glycolysis and the TCA cycle. Dietary carbohydrates are broken down into pyruvate via glycolysis; in patients with pyruvate dehydrogenase deficiency, the lack of enzymatic activity leads to a **buildup of pyruvate**, which is shunted to lactate via lactate dehydrogenase, generating a potentially life-threatening **lactic acidosis**.

Disease management involves the implementation of a **ketogenic diet**: a high-fat, low-carbohydrate diet with



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Disease management involves the implementation of a **ketogenic diet**: a high-fat, low-carbohydrate diet with moderate levels of protein. This diet forces the production of ketone bodies from fat and amino acid catabolism to fuel the body in the place of glucose. The near-absence of glucose in the diet decreases the amount of pyruvate generated, thereby decreasing lactate levels.

Amino acid catabolism results in formation of intermediates that are referred to as glucogenic, ketogenic, or both. Glucogenic amino acid metabolism produces pyruvate or TCA cycle intermediates, which can be converted to glucose via gluconeogenesis. Ketogenic amino acid metabolism generates the ketone body precursor acetyl-CoA. **Lysine** and **leucine** are **exclusively ketogenic** amino acids; they cannot be metabolized to pyruvate and consumption will not lead to increased production of lactic acid.

(Choices A and F) The non-essential glucogenic amino acids alanine and serine can be converted to pyruvate through a transamination reaction catalyzed by alanine transaminase and a deamination reaction catalyzed by serine dehydratase, respectively.

(Choice B) Asparagine is catabolized to aspartate and subsequently transaminated to produce glutamate and oxaloacetate, an intermediate of the TCA cycle. Oxaloacetate by itself cannot be used to produce energy; it must first undergo condensation with acetyl-CoA to form citrate.

(Choice C) The monosaccharide galactose is metabolized in the glycolytic pathway; dietary intake will result in elevated levels of lactate in patients with pyruvate dehydrogenase deficiency.

(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a substrate to form pyruvate and, subsequently, lactate.

Item 19 of 40
Question Id: 998
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:32
My Notebook
Flashcards
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Suspend
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(Choice B) Asparagine is catabolized to aspartate and subsequently transaminated to produce glutamate and oxaloacetate, an intermediate of the TCA cycle. Oxaloacetate by itself cannot be used to produce energy; it must first undergo condensation with acetyl-CoA to form citrate.

(Choice C) The monosaccharide galactose is metabolized in the glycolytic pathway; dietary intake will result in elevated levels of lactate in patients with pyruvate dehydrogenase deficiency.

(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a substrate to form pyruvate and, subsequently, lactate.

Educational objective:

Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and neurologic defects. Patients are unable to convert pyruvate to acetyl-CoA, resulting in a shunting of pyruvate to lactic acid. In these patients, metabolism of exclusively ketogenic amino acids (eg, lysine, leucine) can provide energy in the form of acetyl-CoA without increasing lactate production.

References

- Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations.

Biochemistry	Biochemistry (General Principles)	Tca cycle
Subject	System	Topic

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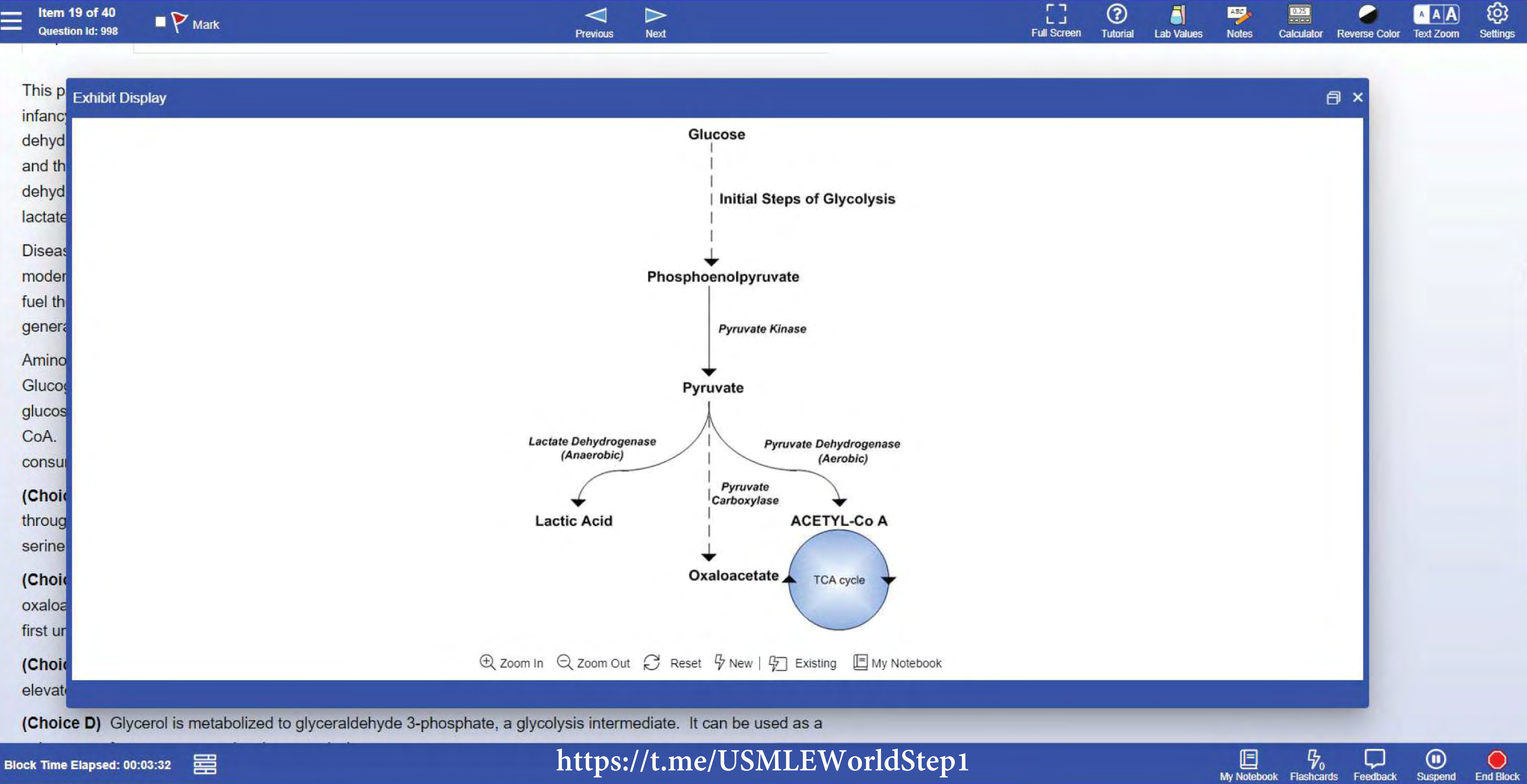
Item 19 of 40
Question Id: 998
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Glucose
Initial Steps of Glycolysis
Phosphoenolpyruvate
Pyruvate Kinase
Pyruvate
Lactate Dehydrogenase (Anaerobic)
Pyruvate Dehydrogenase (Aerobic)
Pyruvate Carboxylase
Lactic Acid
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(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a

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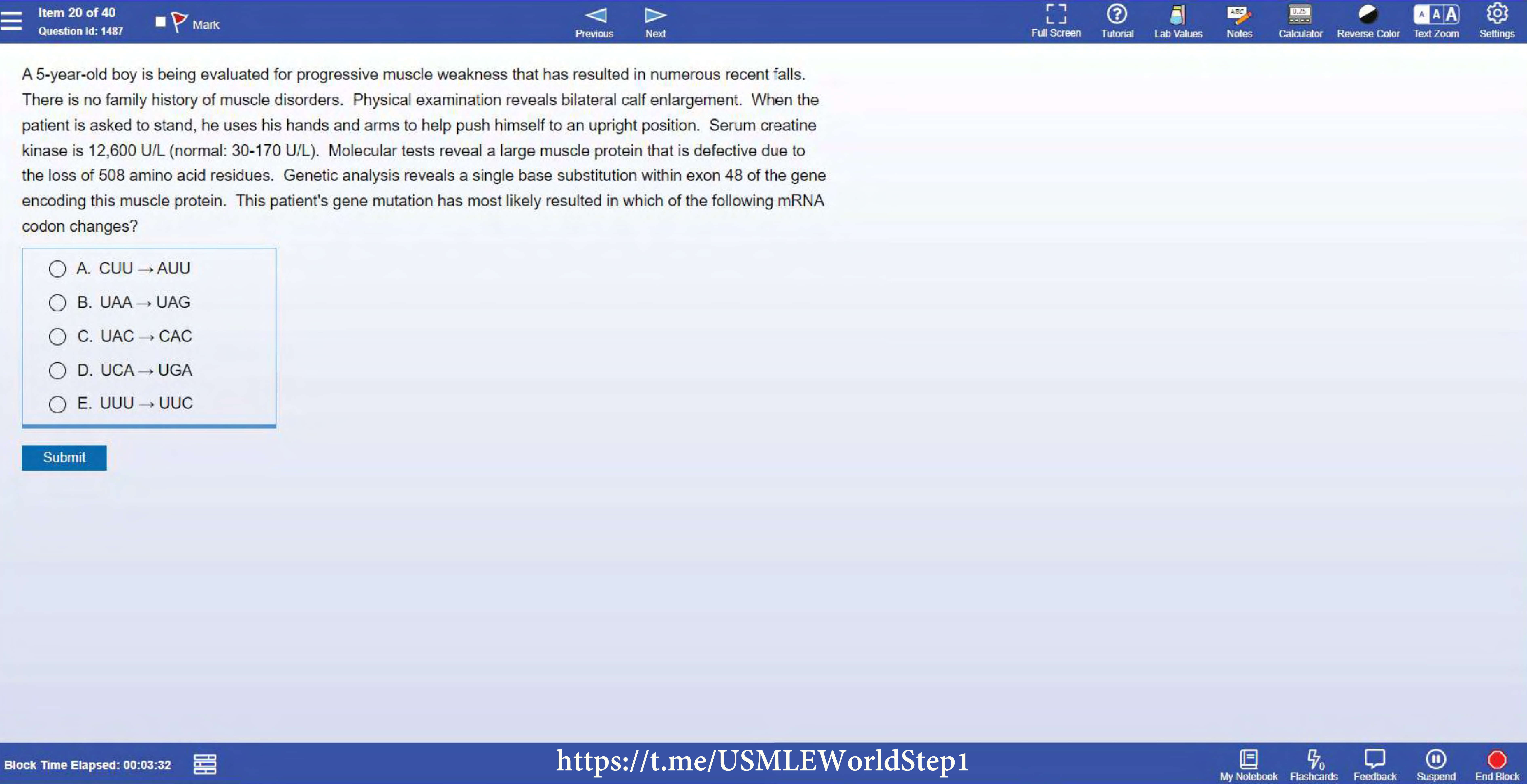
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 20 of 40
Question Id: 1487

A 5-year-old boy is being evaluated for progressive muscle weakness that has resulted in numerous recent falls. There is no family history of muscle disorders. Physical examination reveals bilateral calf enlargement. When the patient is asked to stand, he uses his hands and arms to help push himself to an upright position. Serum creatine kinase is 12,600 U/L (normal: 30-170 U/L). Molecular tests reveal a large muscle protein that is defective due to the loss of 508 amino acid residues. Genetic analysis reveals a single base substitution within exon 48 of the gene encoding this muscle protein. This patient's gene mutation has most likely resulted in which of the following mRNA codon changes?

○ A. CUU → AUU
○ B. UAA → UAG
○ C. UAC → CAC
○ D. UCA → UGA
○ E. UUU → UUC

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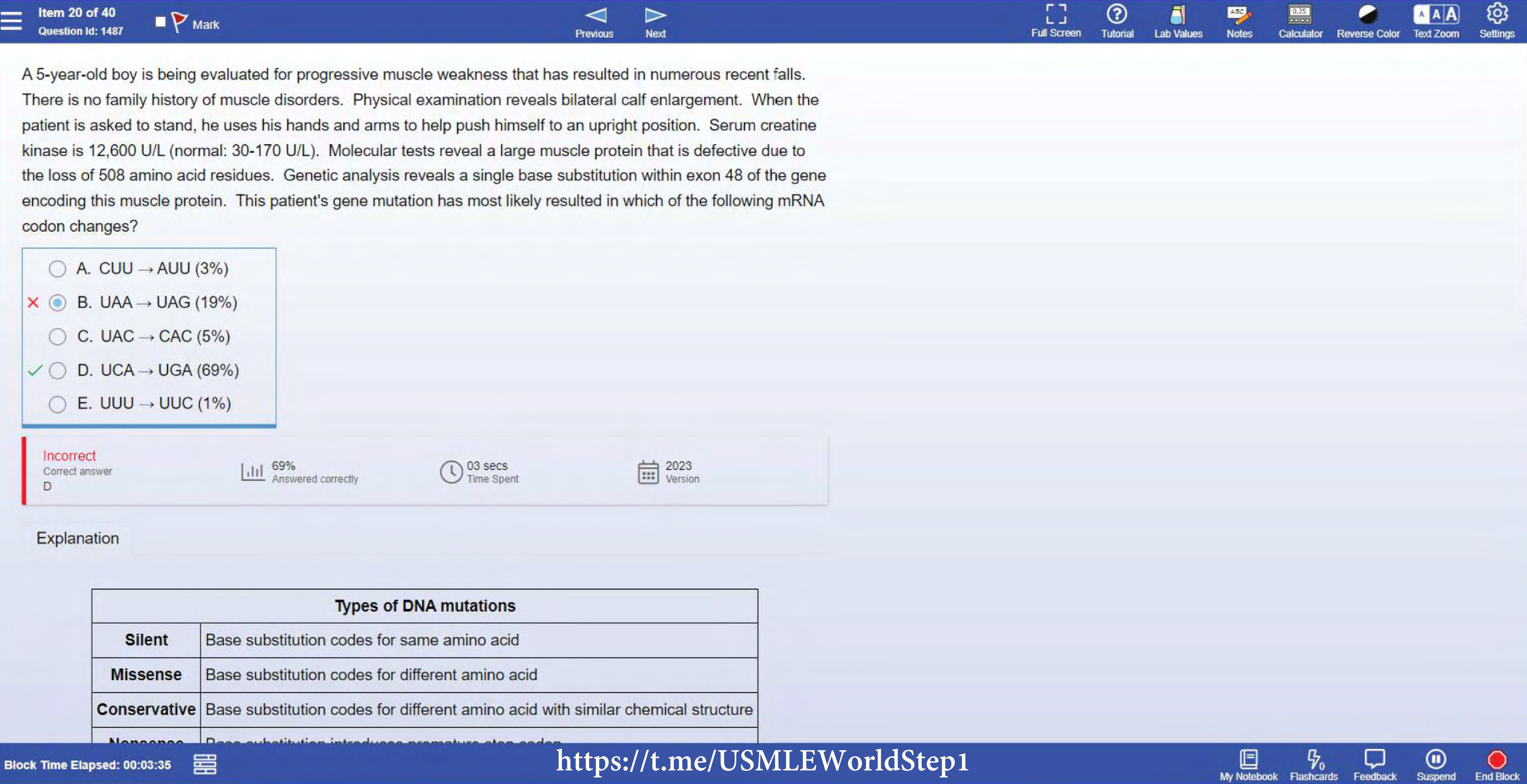
Item 20 of 40
Question Id: 1487
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:35
My Notebook
Flashcards
Feedback
Suspend
End Block

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- ○ A. CUU → AUU (3%)
- ✗ ● B. UAA → UAG (19%)
- ○ C. UAC → CAC (5%)
- ✓ ○ D. UCA → UGA (69%)
- ○ E. UUU → UUC (1%)

Incorrect
Correct answer
D

69%
Answered correctly

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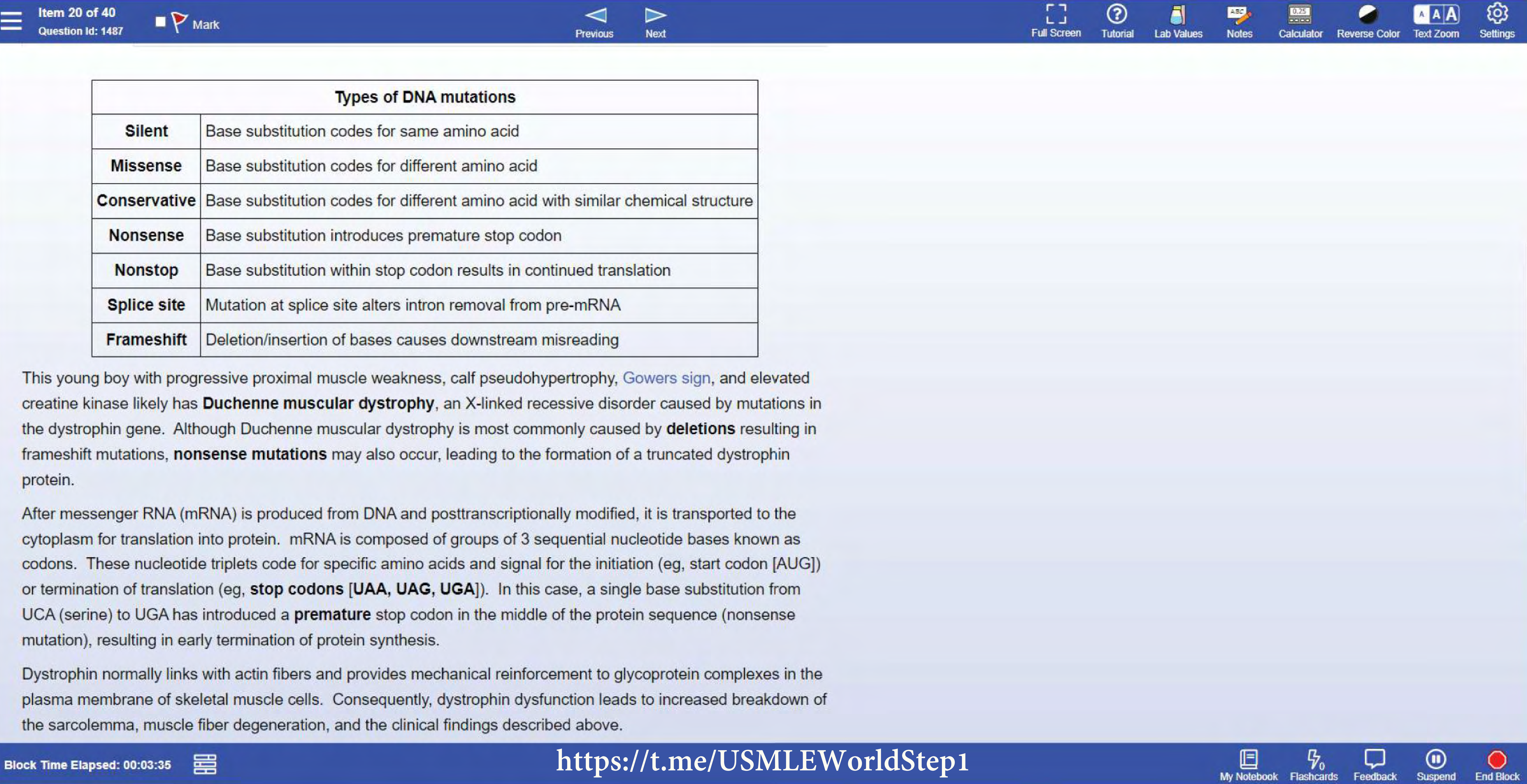
2023
Version

Explanation

Types of DNA mutations	
Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon


Item 20 of 40
Question Id: 1487
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:03:35
My Notebook
Flashcards
Feedback
Suspend
End Block

Types of DNA mutations	
Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon
Nonstop	Base substitution within stop codon results in continued translation
Splice site	Mutation at splice site alters intron removal from pre-mRNA
Frameshift	Deletion/insertion of bases causes downstream misreading

This young boy with progressive proximal muscle weakness, calf pseudohypertrophy, Gowers sign, and elevated creatine kinase likely has **Duchenne muscular dystrophy**, an X-linked recessive disorder caused by mutations in the dystrophin gene. Although Duchenne muscular dystrophy is most commonly caused by **deletions** resulting in frameshift mutations, **nonsense mutations** may also occur, leading to the formation of a truncated dystrophin protein.

After messenger RNA (mRNA) is produced from DNA and posttranscriptionally modified, it is transported to the cytoplasm for translation into protein. mRNA is composed of groups of 3 sequential nucleotide bases known as codons. These nucleotide triplets code for specific amino acids and signal for the initiation (eg, start codon [AUG]) or termination of translation (eg, **stop codons** [**UAA, UAG, UGA**]). In this case, a single base substitution from UCA (serine) to UGA has introduced a **premature** stop codon in the middle of the protein sequence (nonsense mutation), resulting in early termination of protein synthesis.

Dystrophin normally links with actin fibers and provides mechanical reinforcement to glycoprotein complexes in the plasma membrane of skeletal muscle cells. Consequently, dystrophin dysfunction leads to increased breakdown of the sarcolemma, muscle fiber degeneration, and the clinical findings described above.

Item 20 of 40
Question Id: 1487
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Dystrophin normally links with actin fibers and provides mechanical reinforcement to glycoprotein complexes in the plasma membrane of skeletal muscle cells. Consequently, dystrophin dysfunction leads to increased breakdown of the sarcolemma, muscle fiber degeneration, and the clinical findings described above.

(Choices A and C) Changing CUU (leucine) to AUU (isoleucine) or UAC (tyrosine) to CAC (histidine) would result in an amino acid substitution at one position (missense mutation). The function of this protein may be altered depending on a variety of factors, but the ultimate size of the protein will remain the same. Missense mutations that result in the substitution of a new amino acid with similar chemical properties are called conservative mutations.

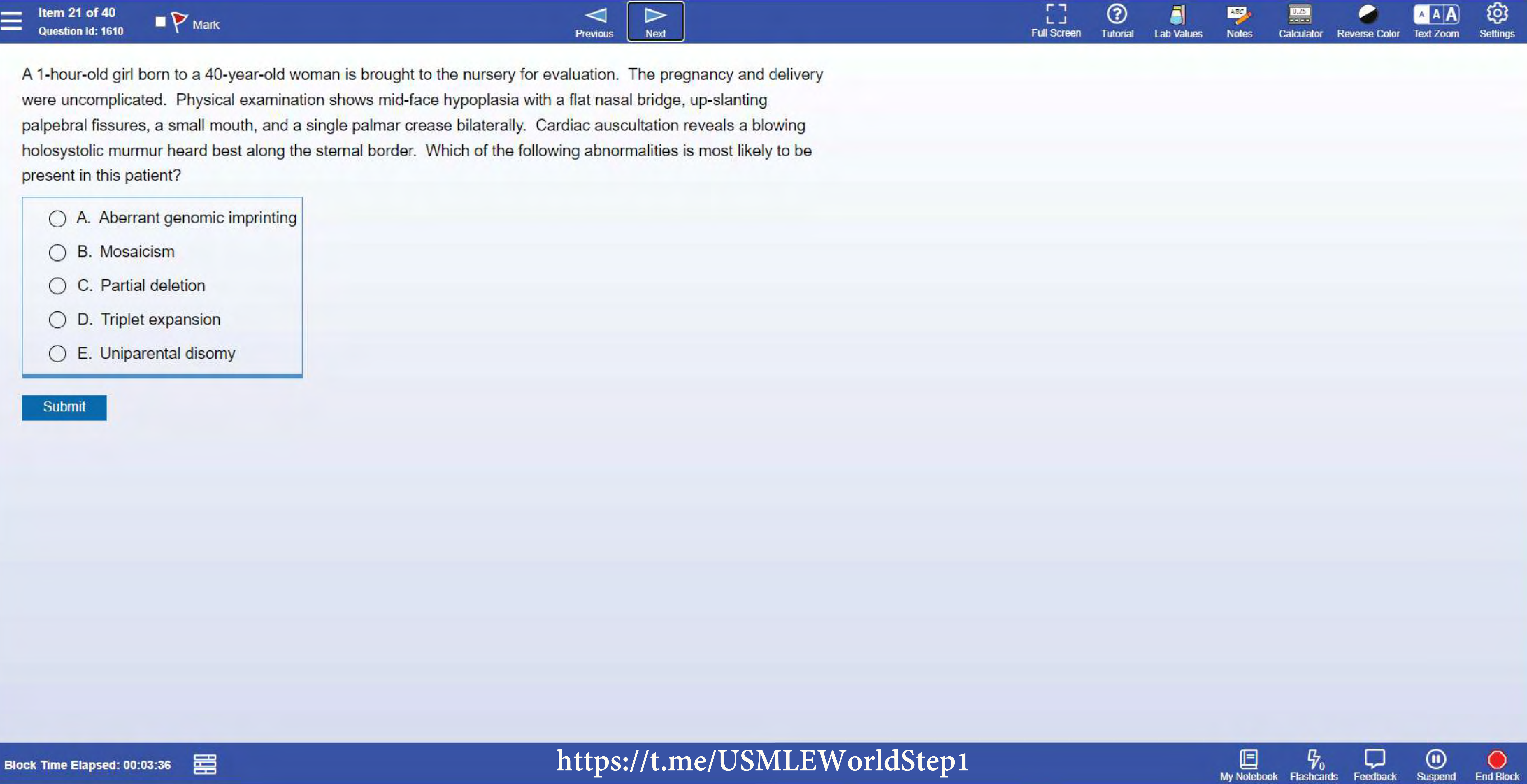
(Choice B) Changing UAA to UAG would not affect protein structure or function because both of these sequences are stop codons. Stop codons are normally located at the end of the translated region of mRNA.

(Choice E) Changing UUU to UUC would not affect the protein as both sequences code for phenylalanine. Point mutations that do not change the amino acid sequence of a protein are called silent mutations.

Educational objective:

Duchenne muscular dystrophy presents with progressive proximal muscle weakness in young boys due to increased muscle fiber degeneration. It is caused by frameshift mutations (most common) or nonsense mutations in the dystrophin gene that lead to the formation of a truncated, defective protein. Nonsense mutations introduce premature stop codons (eg, UAA, UAG, UGA) in the coding sequence of mRNA.

References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Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 21 of 40
Question Id: 1610

A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face hypoplasia with a flat nasal bridge, up-slanting palpebral fissures, a small mouth, and a single palmar crease bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

○ A. Aberrant genomic imprinting
○ B. Mosaicism
○ C. Partial deletion
○ D. Triplet expansion
○ E. Uniparental disomy

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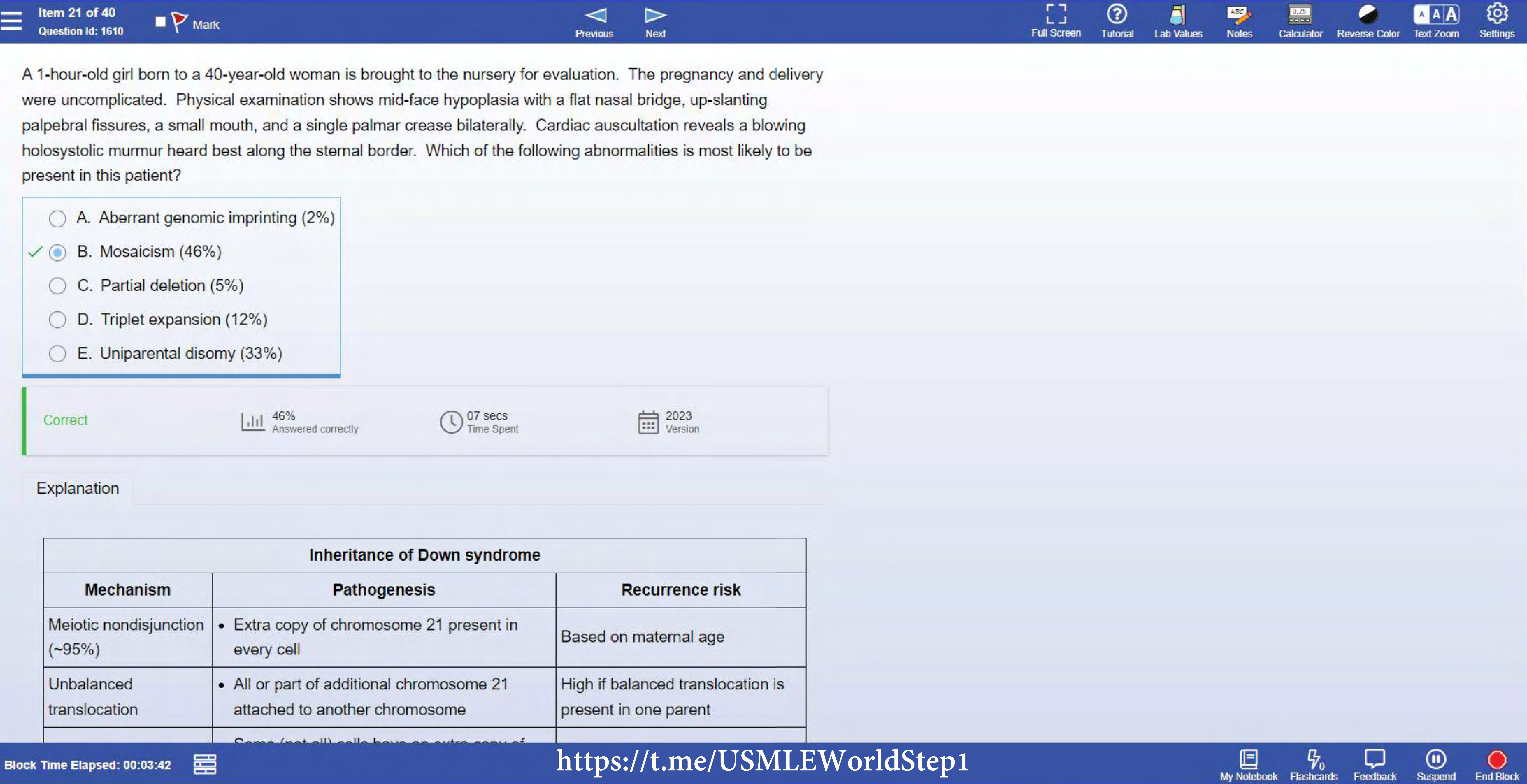
Item 21 of 40
Question Id: 1610
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Aberrant genomic imprinting (2%)

✓ ● B. Mosaicism (46%)

○ C. Partial deletion (5%)

○ D. Triplet expansion (12%)

○ E. Uniparental disomy (33%)

Correct

46% Answered correctly

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2023 Version

Explanation

Inheritance of Down syndrome

Mechanism	Pathogenesis	Recurrence risk
Meiotic nondisjunction (~95%)	• Extra copy of chromosome 21 present in every cell	Based on maternal age
Unbalanced translocation	• All or part of additional chromosome 21 attached to another chromosome	High if balanced translocation is present in one parent
	• Some (not all) cells have an extra copy of	

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My Notebook
Flashcards
Feedback
Suspend
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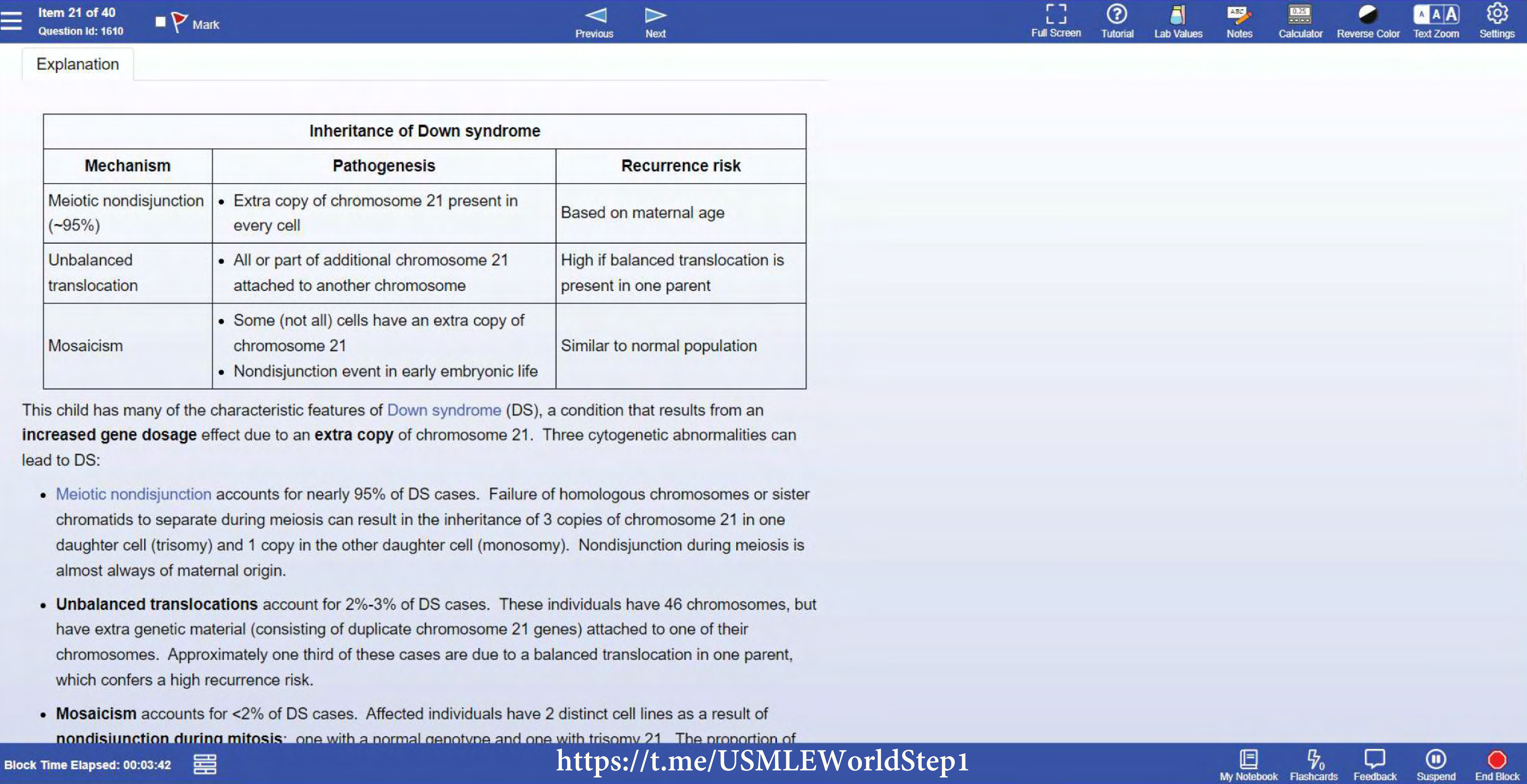
Item 21 of 40
Question Id: 1610
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Inheritance of Down syndrome		
Mechanism	**Pathogenesis**	**Recurrence risk**
Meiotic nondisjunction (~95%)	- Extra copy of chromosome 21 present in every cell	Based on maternal age
Unbalanced translocation	- All or part of additional chromosome 21 attached to another chromosome	High if balanced translocation is present in one parent
Mosaicism	- Some (not all) cells have an extra copy of chromosome 21 - Nondisjunction event in early embryonic life	Similar to normal population

This child has many of the characteristic features of Down syndrome (DS), a condition that results from an **increased gene dosage** effect due to an **extra copy** of chromosome 21. Three cytogenetic abnormalities can lead to DS:

- Meiotic nondisjunction accounts for nearly 95% of DS cases. Failure of homologous chromosomes or sister chromatids to separate during meiosis can result in the inheritance of 3 copies of chromosome 21 in one daughter cell (trisomy) and 1 copy in the other daughter cell (monosomy). Nondisjunction during meiosis is almost always of maternal origin.
- **Unbalanced translocations** account for 2%-3% of DS cases. These individuals have 46 chromosomes, but have extra genetic material (consisting of duplicate chromosome 21 genes) attached to one of their chromosomes. Approximately one third of these cases are due to a balanced translocation in one parent, which confers a high recurrence risk.
- **Mosaicism** accounts for <2% of DS cases. Affected individuals have 2 distinct cell lines as a result of **nondisjunction during mitosis**: one with a normal genotype and one with trisomy 21. The proportion of

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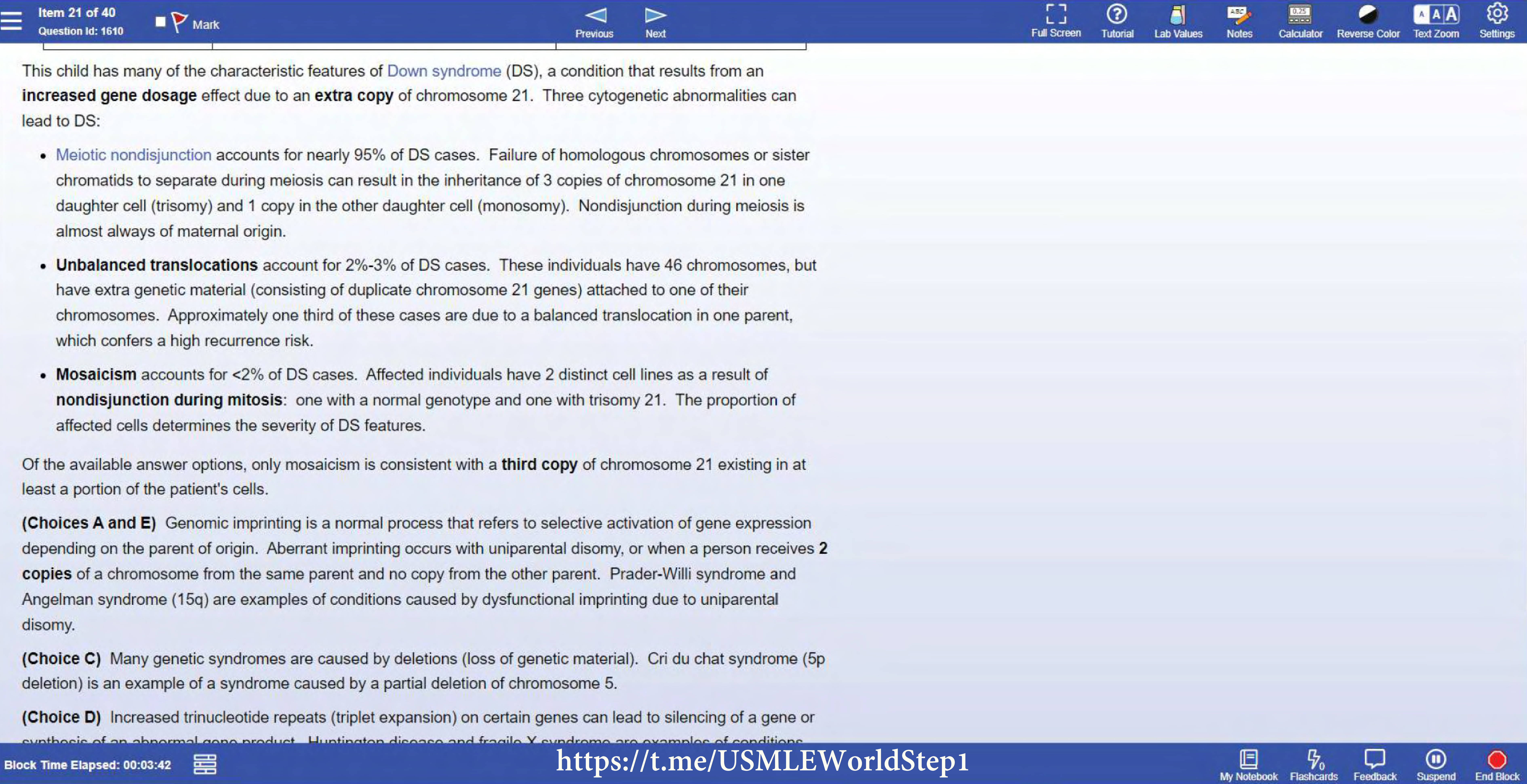
My Notebook
Flashcards
Feedback
Suspend
End Block



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- **Mosaicism** accounts for <2% of DS cases. Affected individuals have 2 distinct cell lines as a result of **nondisjunction during mitosis**: one with a normal genotype and one with trisomy 21. The proportion of affected cells determines the severity of DS features.

Of the available answer options, only mosaicism is consistent with a **third copy** of chromosome 21 existing in at least a portion of the patient's cells.

(Choices A and E) Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2 copies** of a chromosome from the same parent and no copy from the other parent. Prader-Willi syndrome and Angelman syndrome (15q) are examples of conditions caused by dysfunctional imprinting due to uniparental disomy.

(Choice C) Many genetic syndromes are caused by deletions (loss of genetic material). Cri du chat syndrome (5p deletion) is an example of a syndrome caused by a partial deletion of chromosome 5.

(Choice D) Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions

Item 21 of 40
Question Id: 1610
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choice D) Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions caused by triplet expansion.

Educational objective:

Common findings in Down syndrome include cognitive impairment, facial dysmorphism, and cardiac defects; 95% of cases are caused by the presence of an extra chromosome 21 (trisomy) resulting from nondisjunction. Unbalanced Robertsonian translocations or mosaicism are less common causes.

References

- A parent's guide to the genetics of Down syndrome.
- Mosaicism for trisomy 21: a review.

Genetics	Genetics (General Principles)	Aneuploidy
Subject	System	Topic

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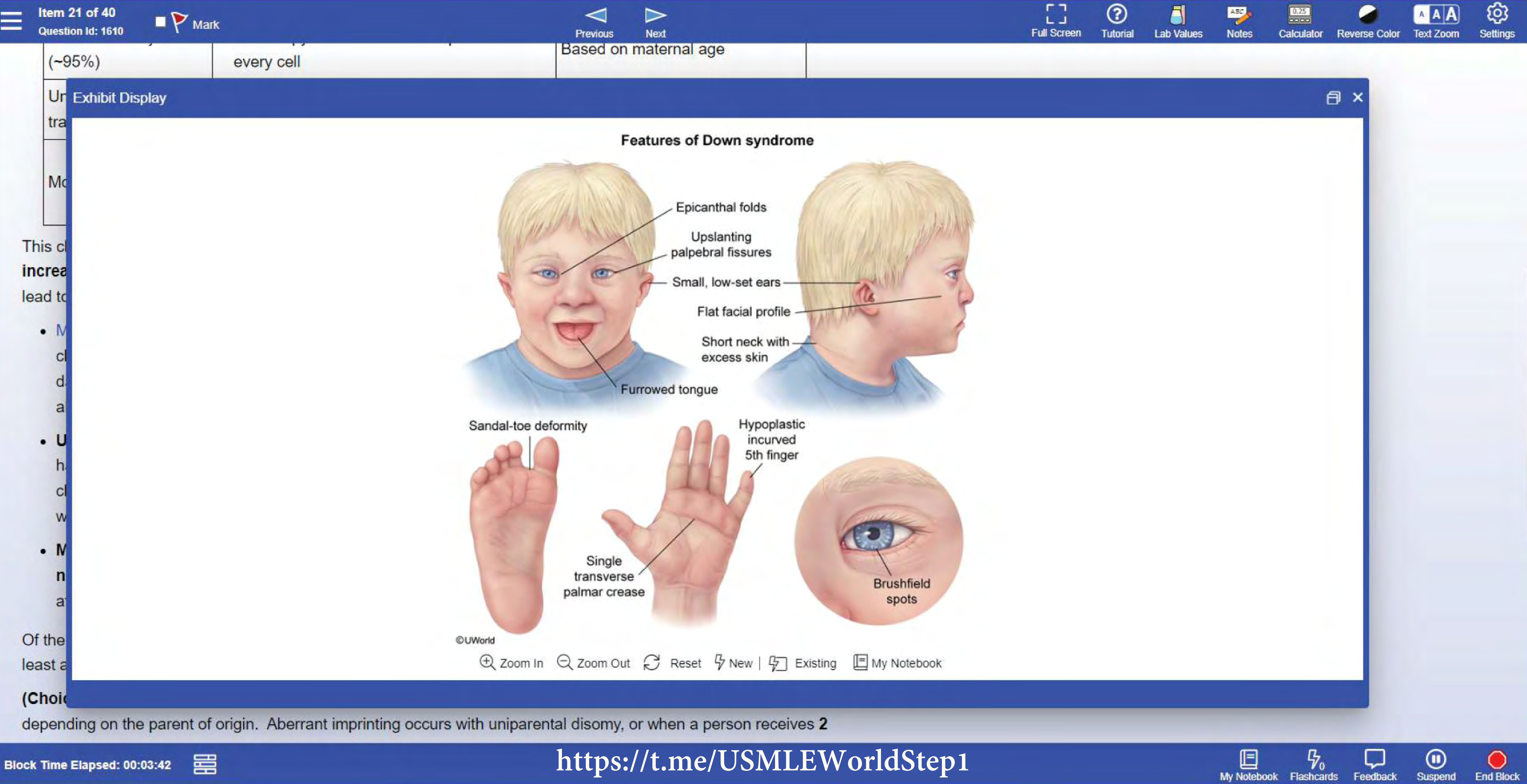
Item 21 of 40
Question Id: 1610
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
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My Notebook
Block Time Elapsed: 00:03:42
My Notebook
Flashcards
Feedback
Suspend
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Features of Down syndrome

Epicanthal folds
Upslanting palpebral fissures
Small, low-set ears
Flat facial profile
Short neck with excess skin
Furrowed tongue
Sandal-toe deformity
Hypoplastic incurved 5th finger
Single transverse palmar crease
Brushfield spots

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(~95%)	every cell	Based on maternal age

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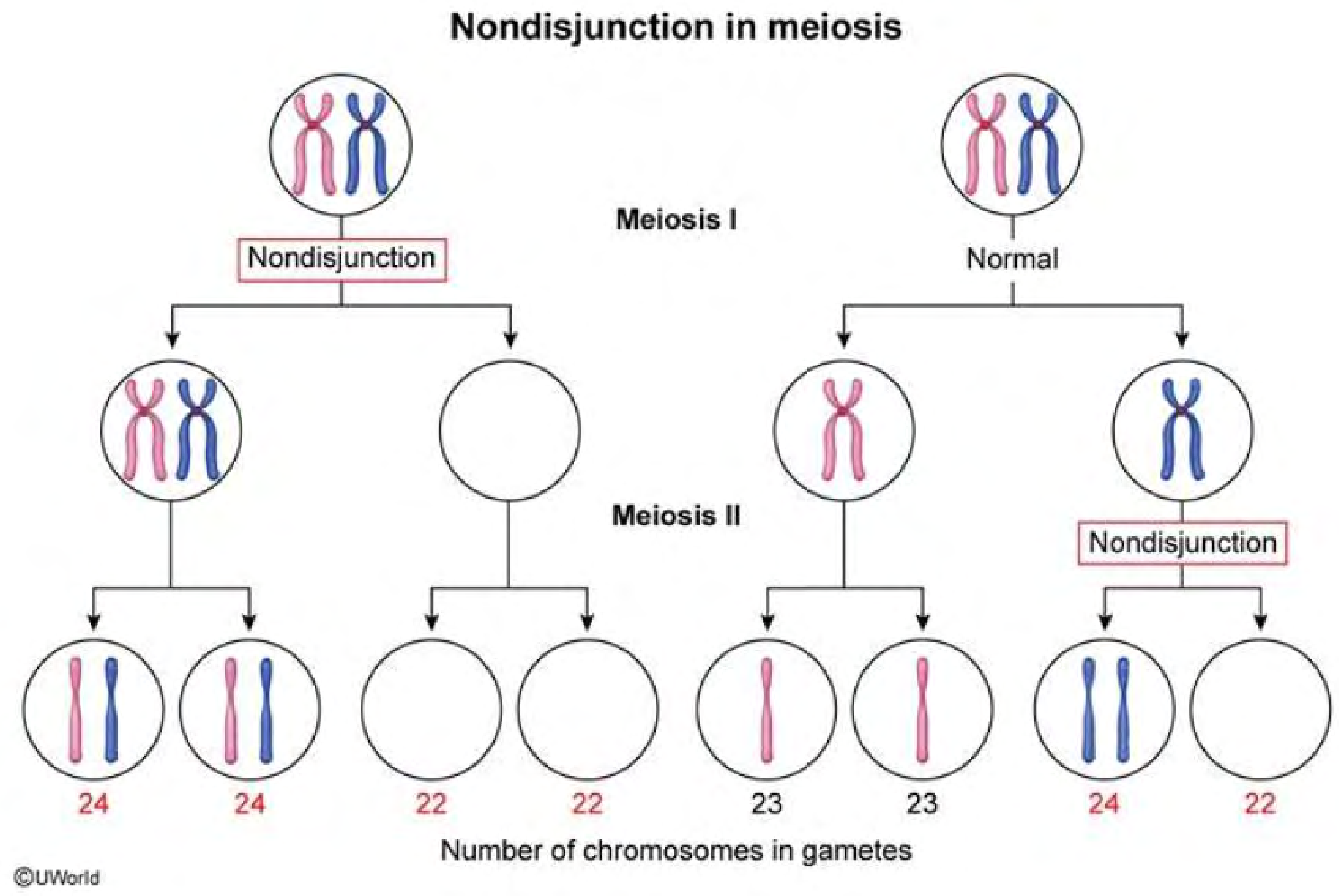
Nondisjunction in meiosis
Meiosis I
Nondisjunction
Normal
Meiosis II
Nondisjunction
24
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Number of chromosomes in gametes
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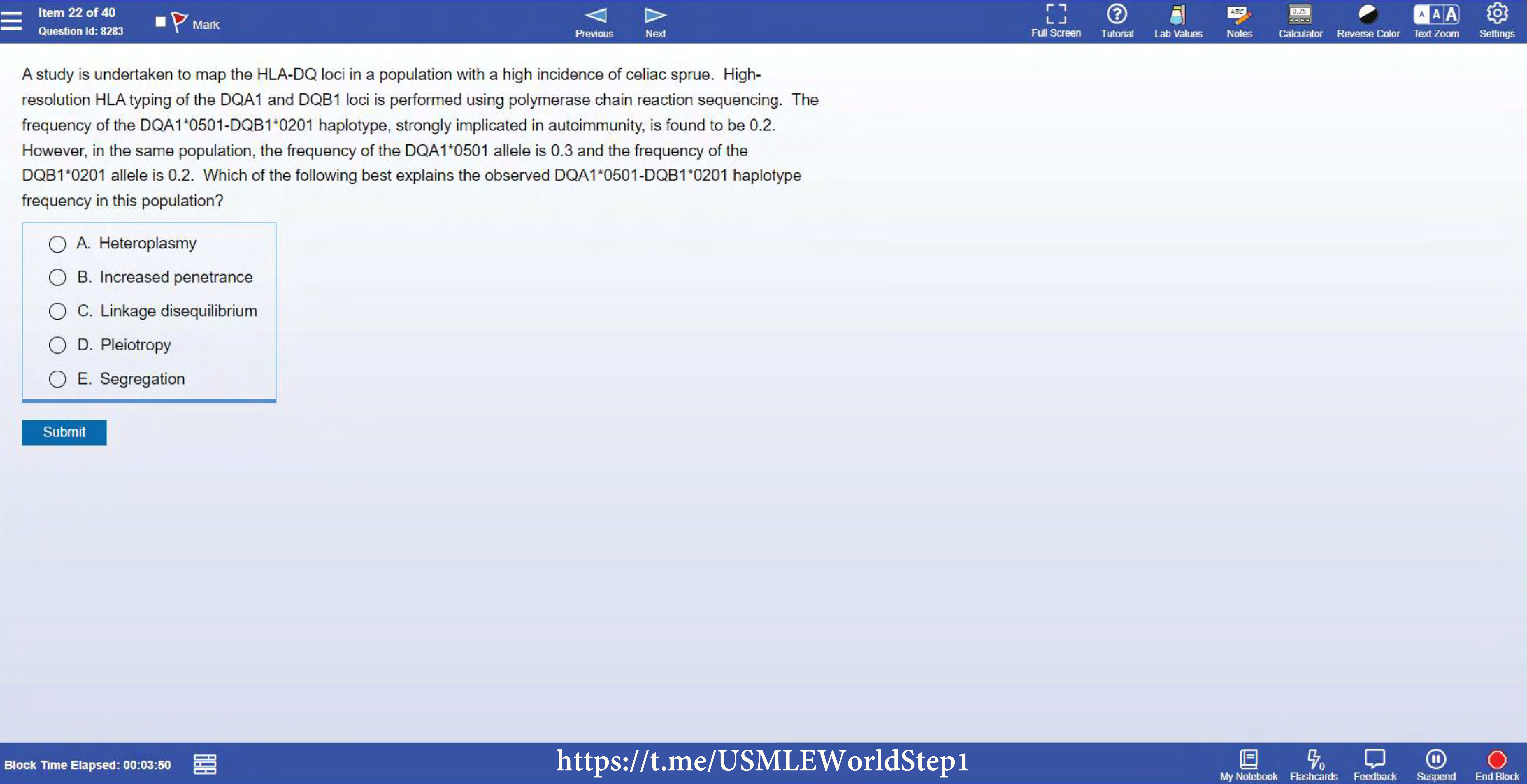
depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2**


Item 22 of 40
Question Id: 8283
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A study is undertaken to map the HLA-DQ loci in a population with a high incidence of celiac sprue. High-resolution HLA typing of the DQA1 and DQB1 loci is performed using polymerase chain reaction sequencing. The frequency of the DQA1*0501-DQB1*0201 haplotype, strongly implicated in autoimmunity, is found to be 0.2. However, in the same population, the frequency of the DQA1*0501 allele is 0.3 and the frequency of the DQB1*0201 allele is 0.2. Which of the following best explains the observed DQA1*0501-DQB1*0201 haplotype frequency in this population?

○ A. Heteroplasmy
○ B. Increased penetrance
○ C. Linkage disequilibrium
○ D. Pleiotropy
○ E. Segregation

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Block Time Elapsed: 00:03:50
My Notebook
Flashcards
Feedback
Suspend
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- ○ A. Heteroplasmy (11%)
- ○ B. Increased penetrance (8%)
- ✓ ● C. Linkage disequilibrium (60%)
- ○ D. Pleiotropy (13%)
- ○ E. Segregation (7%)

Correct

60% Answered correctly

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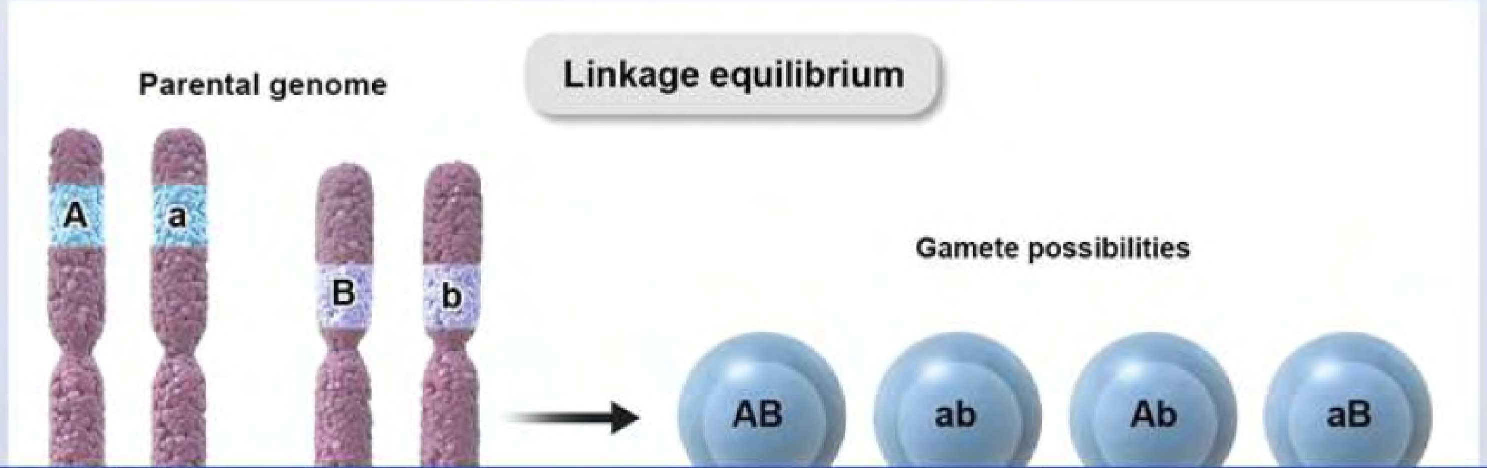
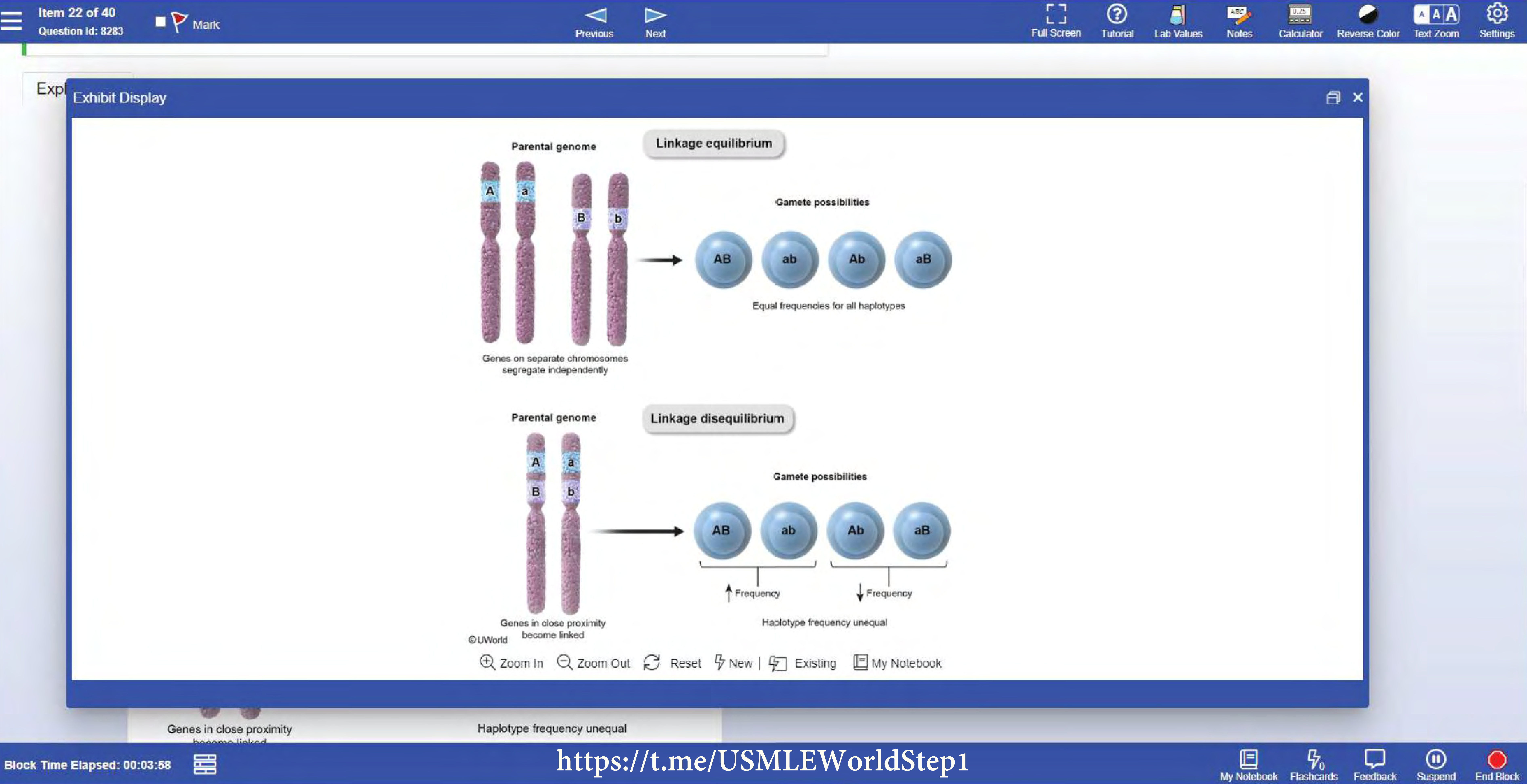
Explanation




Item 22 of 40
Question Id: 8283
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Parental genome
Linkage equilibrium
A
a
B
b
Gamete possibilities
AB
ab
Ab
aB
Equal frequencies for all haplotypes
Genes on separate chromosomes segregate independently
Parental genome
Linkage disequilibrium
A
a
B
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Gamete possibilities
AB
ab
Ab
aB
↑ Frequency
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Haplotype frequency unequal
Genes in close proximity become linked
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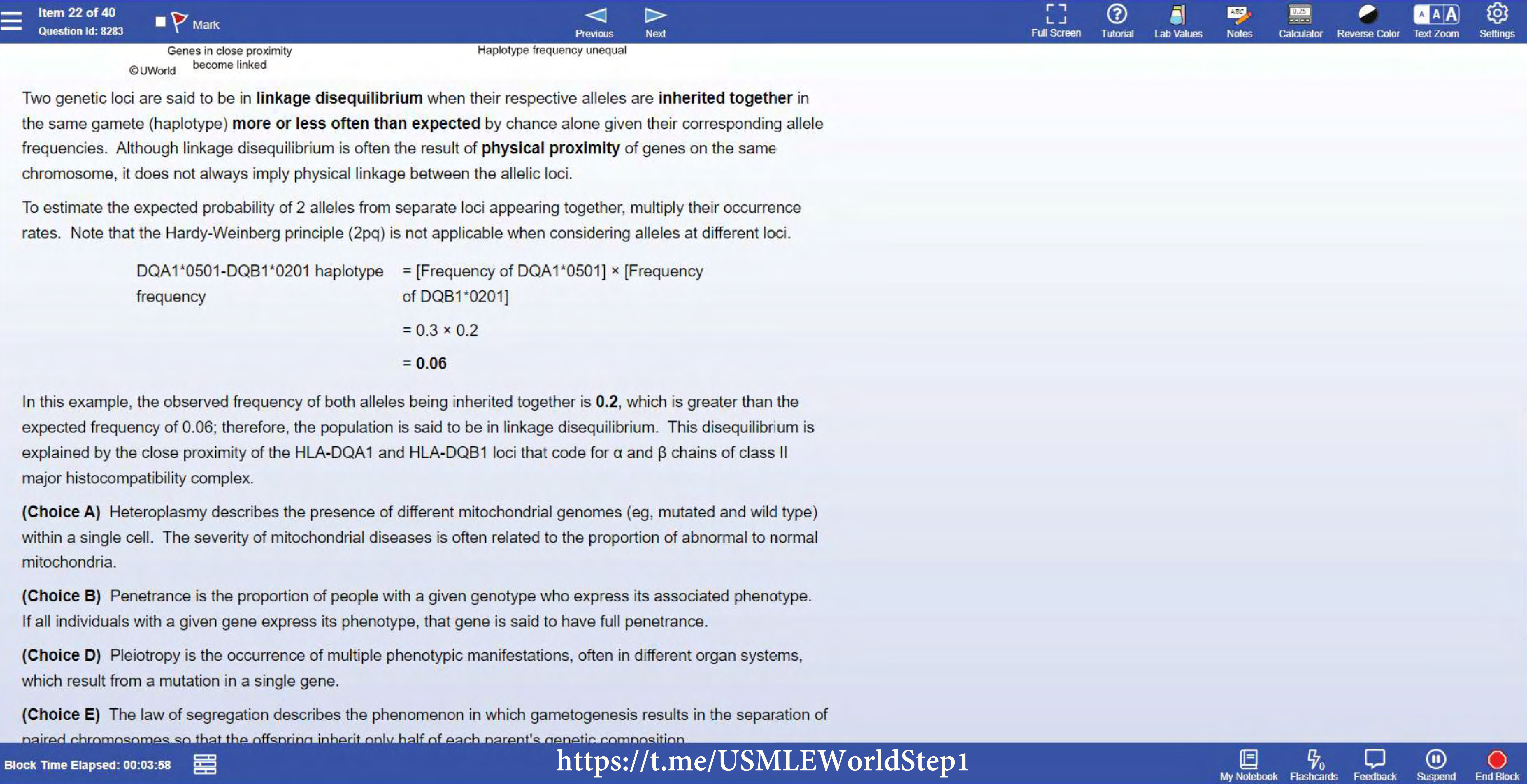
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Genes in close proximity become linked
Haplotype frequency unequal
Block Time Elapsed: 00:03:58
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 22 of 40
Question Id: 8283
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Genes in close proximity become linked
Haplotype frequency unequal
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Two genetic loci are said to be in **linkage disequilibrium** when their respective alleles are **inherited together** in the same gamete (haplotype) **more or less often than expected** by chance alone given their corresponding allele frequencies. Although linkage disequilibrium is often the result of **physical proximity** of genes on the same chromosome, it does not always imply physical linkage between the allelic loci.

To estimate the expected probability of 2 alleles from separate loci appearing together, multiply their occurrence rates. Note that the Hardy-Weinberg principle (2pq) is not applicable when considering alleles at different loci.

DQA1*0501-DQB1*0201 haplotype frequency = [Frequency of DQA1*0501] × [Frequency of DQB1*0201]

= 0.3 × 0.2

= **0.06**

In this example, the observed frequency of both alleles being inherited together is **0.2**, which is greater than the expected frequency of 0.06; therefore, the population is said to be in linkage disequilibrium. This disequilibrium is explained by the close proximity of the HLA-DQA1 and HLA-DQB1 loci that code for α and β chains of class II major histocompatibility complex.

(Choice A) Heteroplasmy describes the presence of different mitochondrial genomes (eg, mutated and wild type) within a single cell. The severity of mitochondrial diseases is often related to the proportion of abnormal to normal mitochondria.

(Choice B) Penetrance is the proportion of people with a given genotype who express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have full penetrance.

(Choice D) Pleiotropy is the occurrence of multiple phenotypic manifestations, often in different organ systems, which result from a mutation in a single gene.

(Choice E) The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

Block Time Elapsed: 00:03:58
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 22 of 40
Question Id: 8283
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

= 0.06

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(Choice E) The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

Educational objective:

Two allele loci are said to be in linkage disequilibrium when a pair of alleles are inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

References

- Gene polymorphisms, inflammatory diseases and cancer.
- Linkage disequilibrium and its expectation in human populations.

Genetics	Genetics (General Principles)	Linkage disequilibrium
Subject	System	Topic

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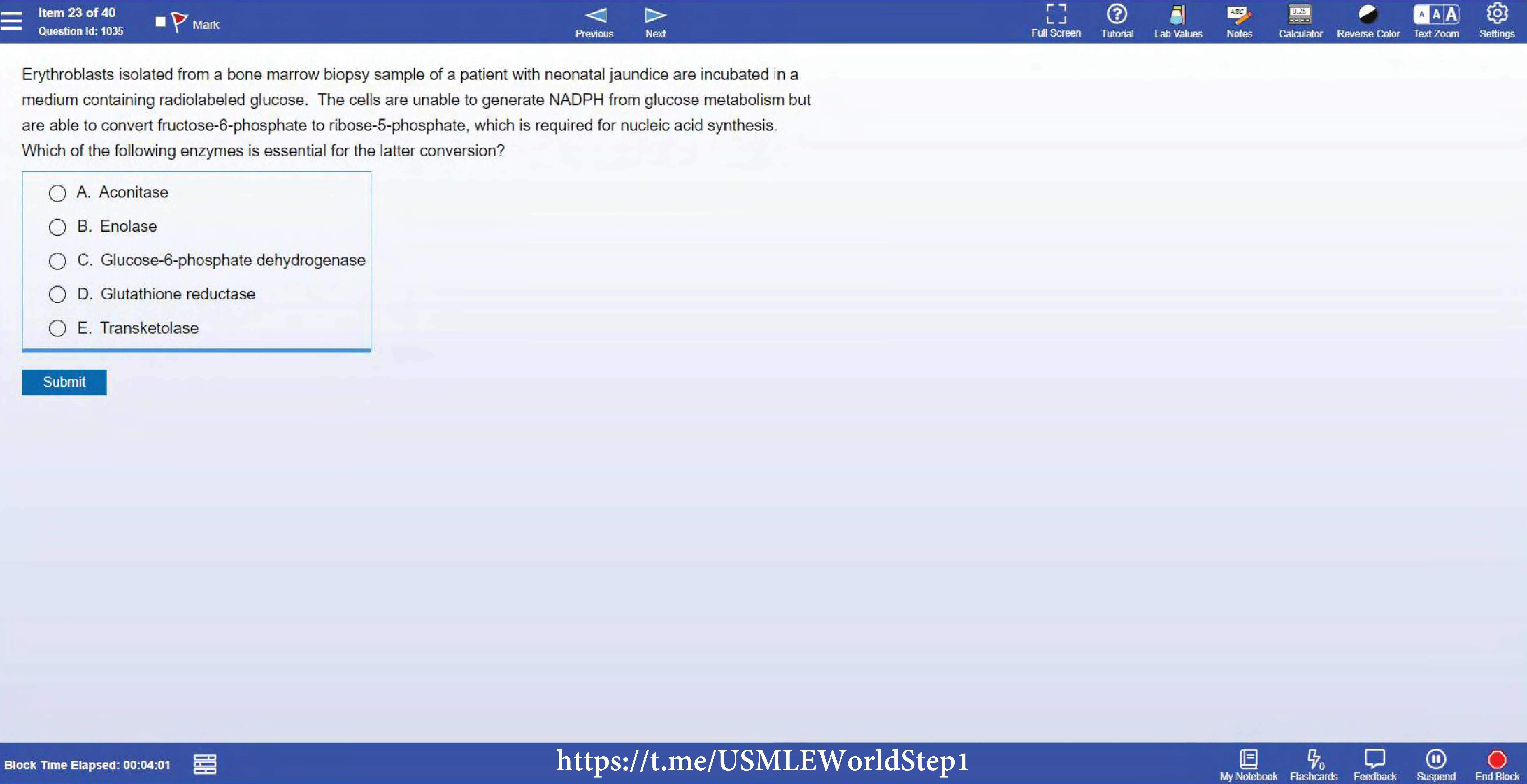

Item 23 of 40
Question Id: 1035
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

○ A. Aconitase
○ B. Enolase
○ C. Glucose-6-phosphate dehydrogenase
○ D. Glutathione reductase
○ E. Transketolase

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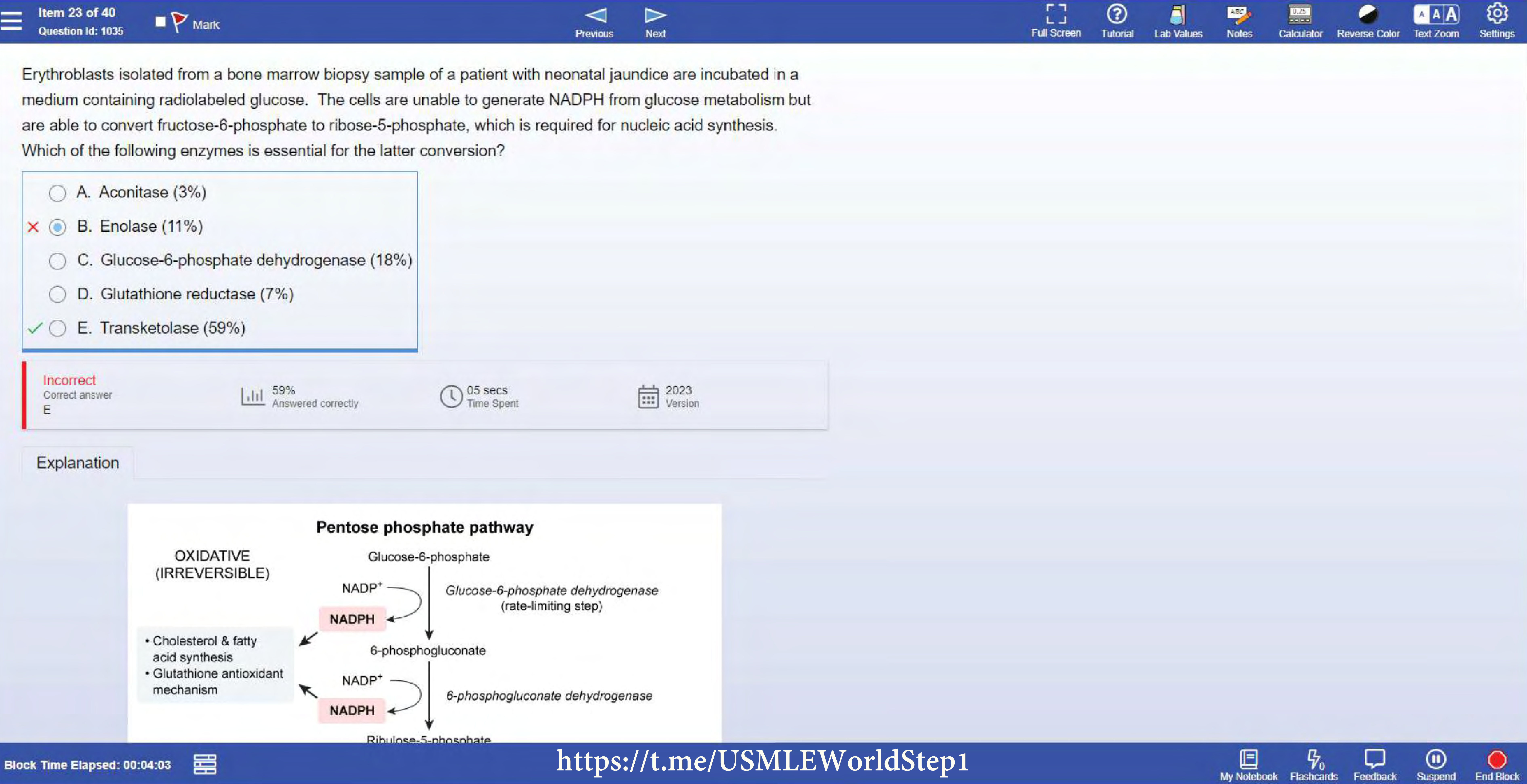
Block Time Elapsed: 00:04:01
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 23 of 40
Question Id: 1035
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Aconitase (3%)

✗ ● B. Enolase (11%)

○ C. Glucose-6-phosphate dehydrogenase (18%)

○ D. Glutathione reductase (7%)

✓ ○ E. Transketolase (59%)

Incorrect
Correct answer
E

59%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Pentose phosphate pathway

OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP+
NADPH
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
• Cholesterol & fatty acid synthesis
• Glutathione antioxidant mechanism
6-phosphogluconate
NADP+
NADPH
6-phosphogluconate dehydrogenase
Ribulose-5-phosphate

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My Notebook
Flashcards
Feedback
Suspend
End Block

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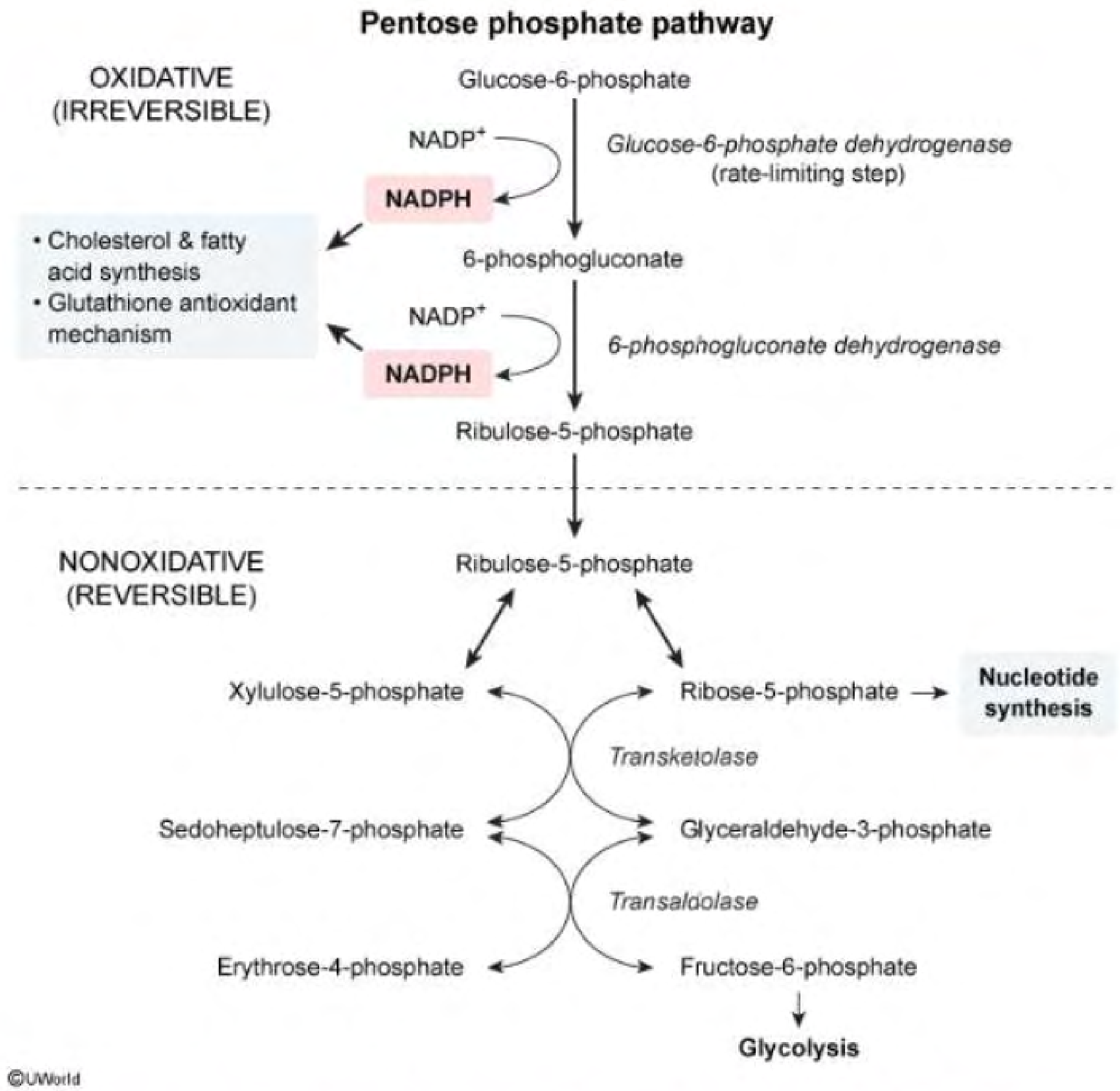
Pentose phosphate pathway
OXIDATIVE
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Glucose-6-phosphate
NADP+
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(rate-limiting step)
• Cholesterol & fatty acid synthesis
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6-phosphogluconate
NADP+
NADPH
6-phosphogluconate dehydrogenase
Ribulose-5-phosphate
NONOXIDATIVE
(REVERSIBLE)
Ribulose-5-phosphate
Xylulose-5-phosphate
Ribose-5-phosphate
Nucleotide synthesis
Transketolase
Sedoheptulose-7-phosphate
Glyceraldehyde-3-phosphate
Transaldolase
Erythrose-4-phosphate
Fructose-6-phosphate
Glycolysis
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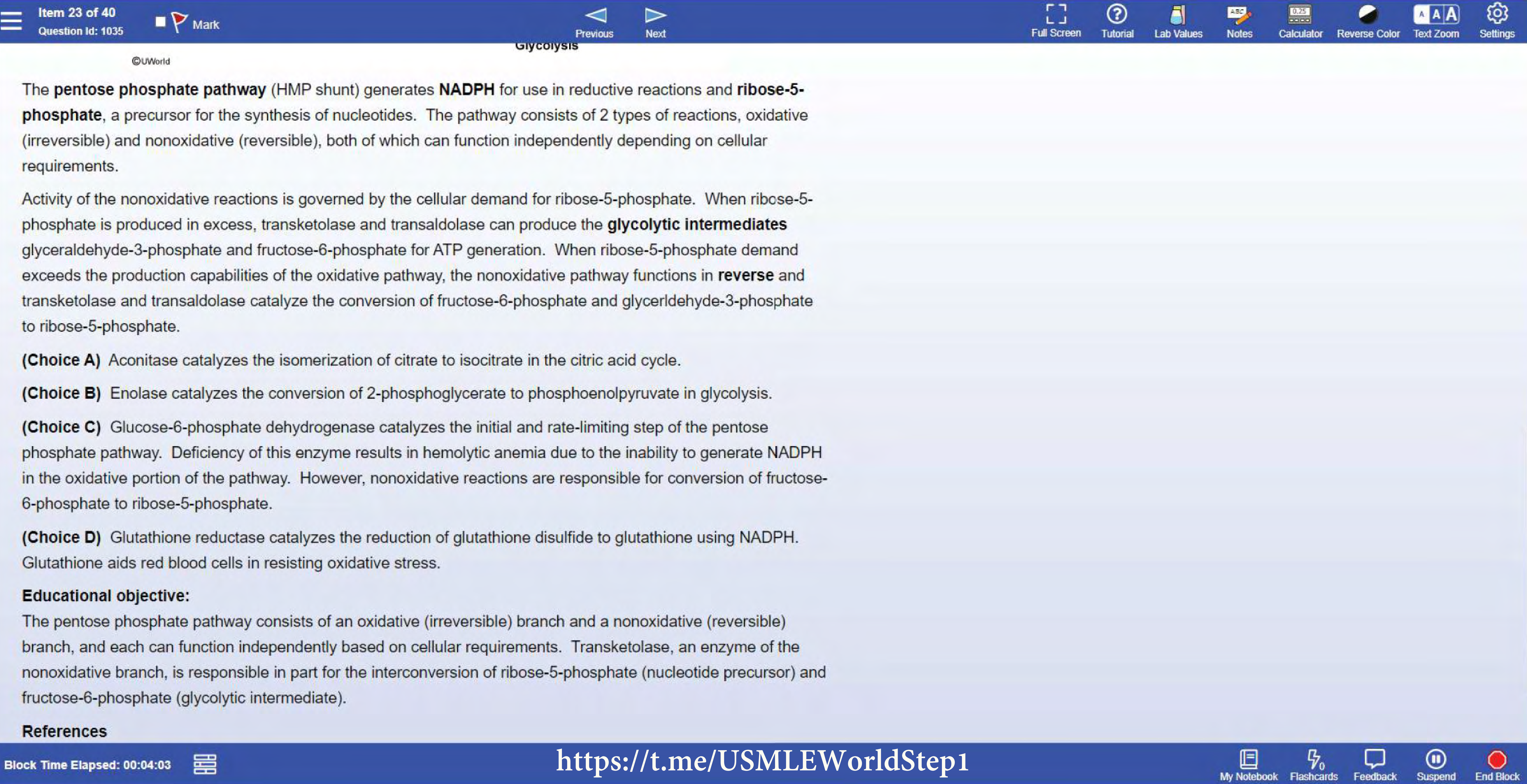
The **pentose phosphate pathway** (HMP shunt) generates **NADPH** for use in reductive reactions and **ribose-5-phosphate**, a precursor for the synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular



The **pentose phosphate pathway** (HMP shunt) generates **NADPH** for use in reductive reactions and **ribose-5-phosphate**, a precursor for the synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular requirements.

Activity of the nonoxidative reactions is governed by the cellular demand for ribose-5-phosphate. When ribose-5-phosphate is produced in excess, transketolase and transaldolase can produce the **glycolytic intermediates** glyceraldehyde-3-phosphate and fructose-6-phosphate for ATP generation. When ribose-5-phosphate demand exceeds the production capabilities of the oxidative pathway, the nonoxidative pathway functions in **reverse** and transketolase and transaldolase catalyze the conversion of fructose-6-phosphate and glycerldehyde-3-phosphate to ribose-5-phosphate.

(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

(Choice B) Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis.

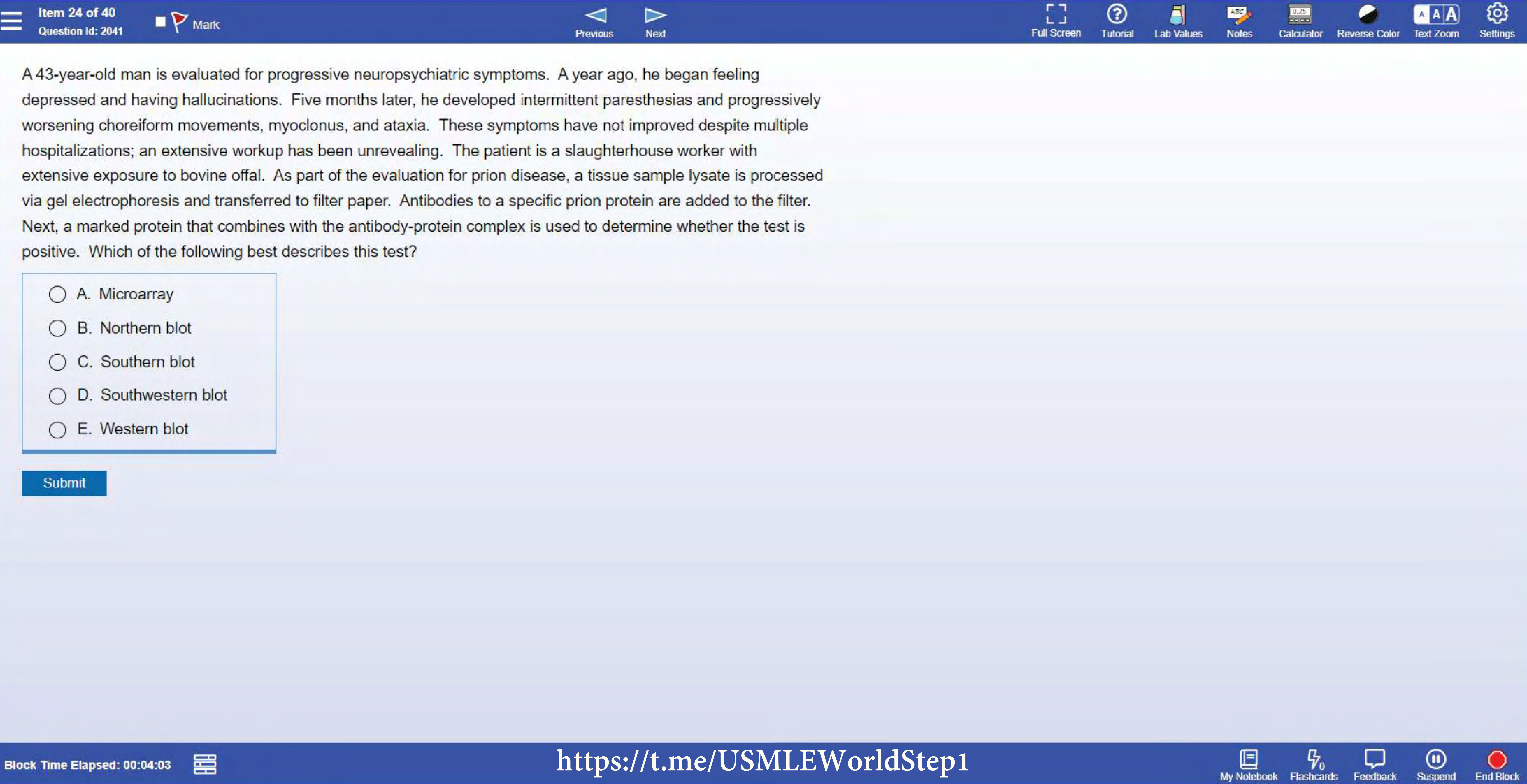
(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate NADPH in the oxidative portion of the pathway. However, nonoxidative reactions are responsible for conversion of fructose-6-phosphate to ribose-5-phosphate.

(Choice D) Glutathione reductase catalyzes the reduction of glutathione disulfide to glutathione using NADPH. Glutathione aids red blood cells in resisting oxidative stress.

Educational objective:

The pentose phosphate pathway consists of an oxidative (irreversible) branch and a nonoxidative (reversible) branch, and each can function independently based on cellular requirements. Transketolase, an enzyme of the nonoxidative branch, is responsible in part for the interconversion of ribose-5-phosphate (nucleotide precursor) and fructose-6-phosphate (glycolytic intermediate).

References


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 24 of 40
Question Id: 2041

A 43-year-old man is evaluated for progressive neuropsychiatric symptoms. A year ago, he began feeling depressed and having hallucinations. Five months later, he developed intermittent paresthesias and progressively worsening choreiform movements, myoclonus, and ataxia. These symptoms have not improved despite multiple hospitalizations; an extensive workup has been unrevealing. The patient is a slaughterhouse worker with extensive exposure to bovine offal. As part of the evaluation for prion disease, a tissue sample lysate is processed via gel electrophoresis and transferred to filter paper. Antibodies to a specific prion protein are added to the filter. Next, a marked protein that combines with the antibody-protein complex is used to determine whether the test is positive. Which of the following best describes this test?

- ○ A. Microarray
- ○ B. Northern blot
- ○ C. Southern blot
- ○ D. Southwestern blot
- ○ E. Western blot

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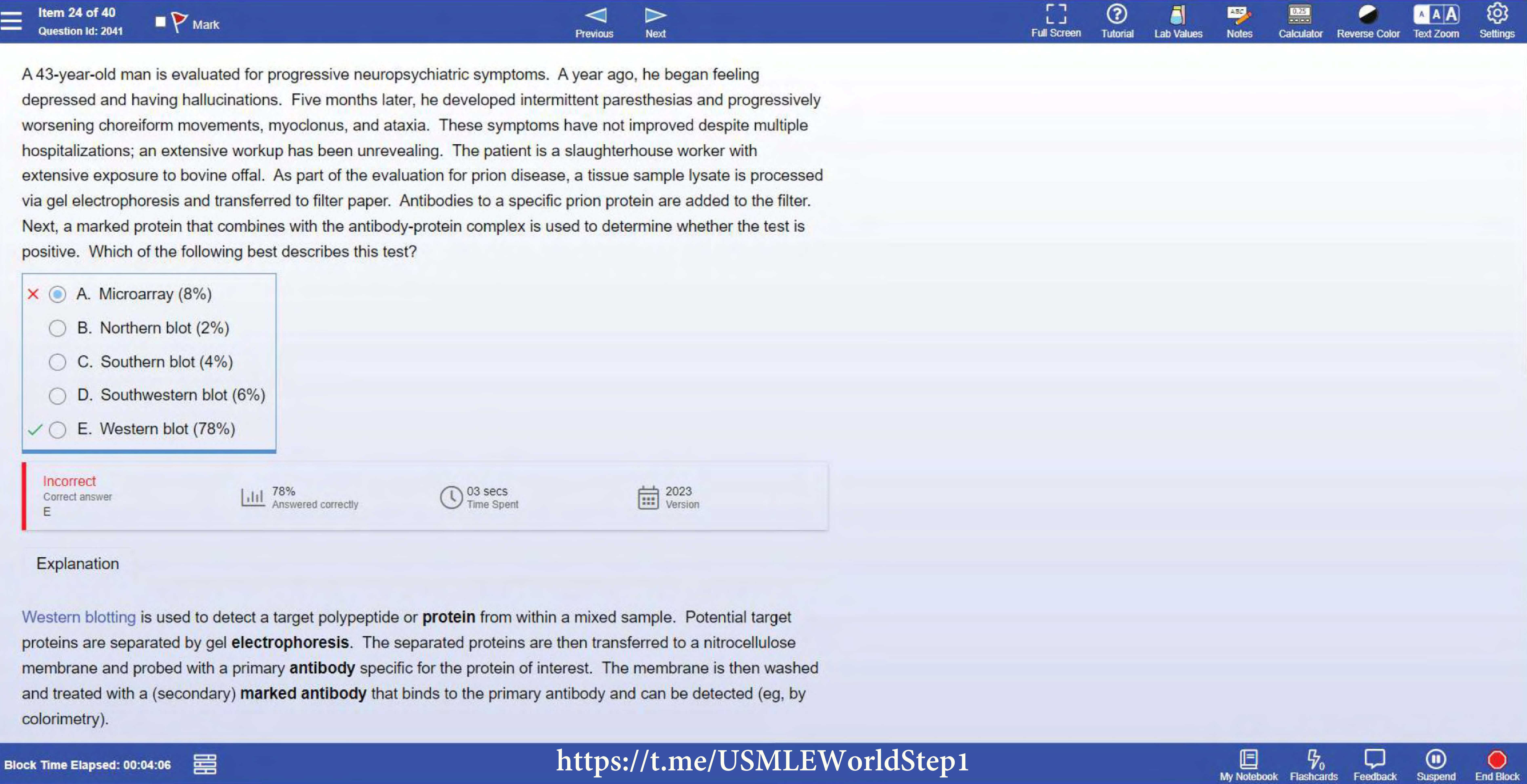
Item 24 of 40
Question Id: 2041
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✗ ● A. Microarray (8%)
- ○ B. Northern blot (2%)
- ○ C. Southern blot (4%)
- ○ D. Southwestern blot (6%)
- ✓ ○ E. Western blot (78%)

Incorrect
Correct answer
E

78%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Western blotting is used to detect a target polypeptide or **protein** from within a mixed sample. Potential target proteins are separated by gel **electrophoresis**. The separated proteins are then transferred to a nitrocellulose membrane and probed with a primary **antibody** specific for the protein of interest. The membrane is then washed and treated with a (secondary) **marked antibody** that binds to the primary antibody and can be detected (eg, by colorimetry).

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Feedback
Suspend
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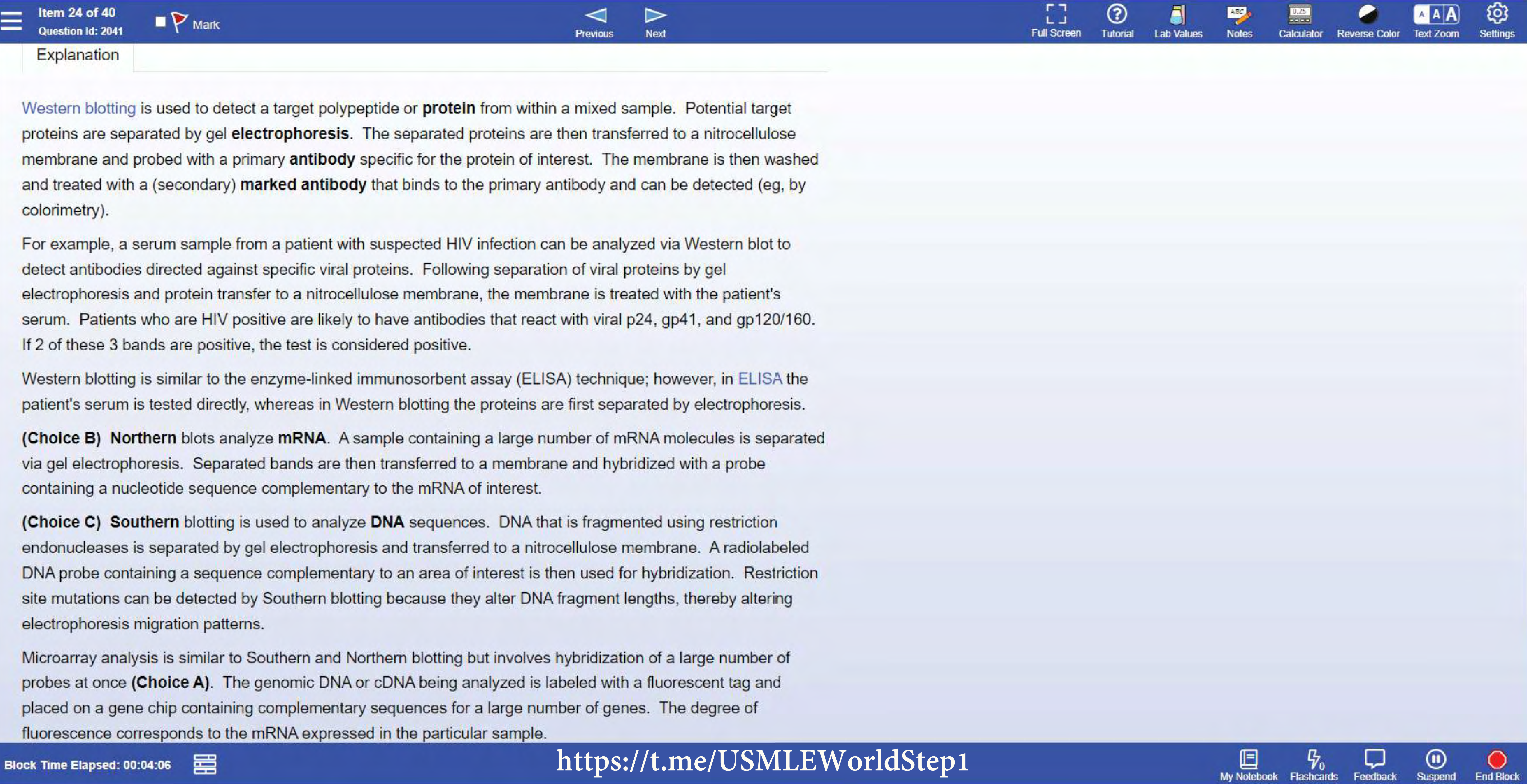


Explanation

Western blotting is used to detect a target polypeptide or **protein** from within a mixed sample. Potential target proteins are separated by gel **electrophoresis**. The separated proteins are then transferred to a nitrocellulose membrane and probed with a primary **antibody** specific for the protein of interest. The membrane is then washed and treated with a (secondary) **marked antibody** that binds to the primary antibody and can be detected (eg, by colorimetry).

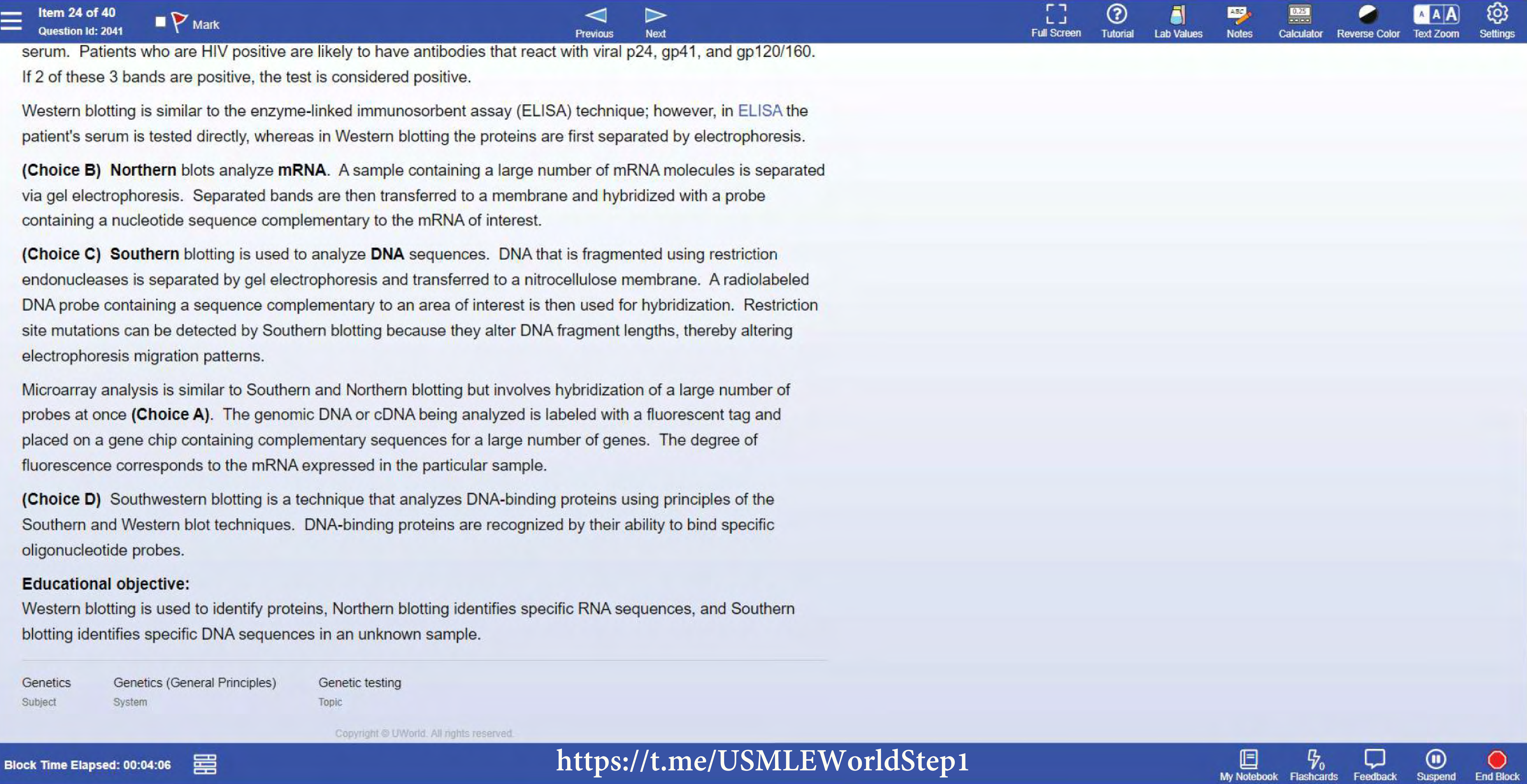
For example, a serum sample from a patient with suspected HIV infection can be analyzed via Western blot to detect antibodies directed against specific viral proteins. Following separation of viral proteins by gel electrophoresis and protein transfer to a nitrocellulose membrane, the membrane is treated with the patient's serum. Patients who are HIV positive are likely to have antibodies that react with viral p24, gp41, and gp120/160. If 2 of these 3 bands are positive, the test is considered positive.

Western blotting is similar to the enzyme-linked immunosorbent assay (ELISA) technique; however, in ELISA the patient's serum is tested directly, whereas in Western blotting the proteins are first separated by electrophoresis.

(Choice B) **Northern** blots analyze **mRNA**. A sample containing a large number of mRNA molecules is separated via gel electrophoresis. Separated bands are then transferred to a membrane and hybridized with a probe containing a nucleotide sequence complementary to the mRNA of interest.

(Choice C) **Southern** blotting is used to analyze **DNA** sequences. DNA that is fragmented using restriction endonucleases is separated by gel electrophoresis and transferred to a nitrocellulose membrane. A radiolabeled DNA probe containing a sequence complementary to an area of interest is then used for hybridization. Restriction site mutations can be detected by Southern blotting because they alter DNA fragment lengths, thereby altering electrophoresis migration patterns.

Microarray analysis is similar to Southern and Northern blotting but involves hybridization of a large number of probes at once **(Choice A)**. The genomic DNA or cDNA being analyzed is labeled with a fluorescent tag and placed on a gene chip containing complementary sequences for a large number of genes. The degree of fluorescence corresponds to the mRNA expressed in the particular sample.



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Microarray analysis is similar to Southern and Northern blotting but involves hybridization of a large number of probes at once **(Choice A)**. The genomic DNA or cDNA being analyzed is labeled with a fluorescent tag and placed on a gene chip containing complementary sequences for a large number of genes. The degree of fluorescence corresponds to the mRNA expressed in the particular sample.

(Choice D) Southwestern blotting is a technique that analyzes DNA-binding proteins using principles of the Southern and Western blot techniques. DNA-binding proteins are recognized by their ability to bind specific oligonucleotide probes.

Educational objective:

Western blotting is used to identify proteins, Northern blotting identifies specific RNA sequences, and Southern blotting identifies specific DNA sequences in an unknown sample.

Genetics	Genetics (General Principles)	Genetic testing
Subject	System	Topic

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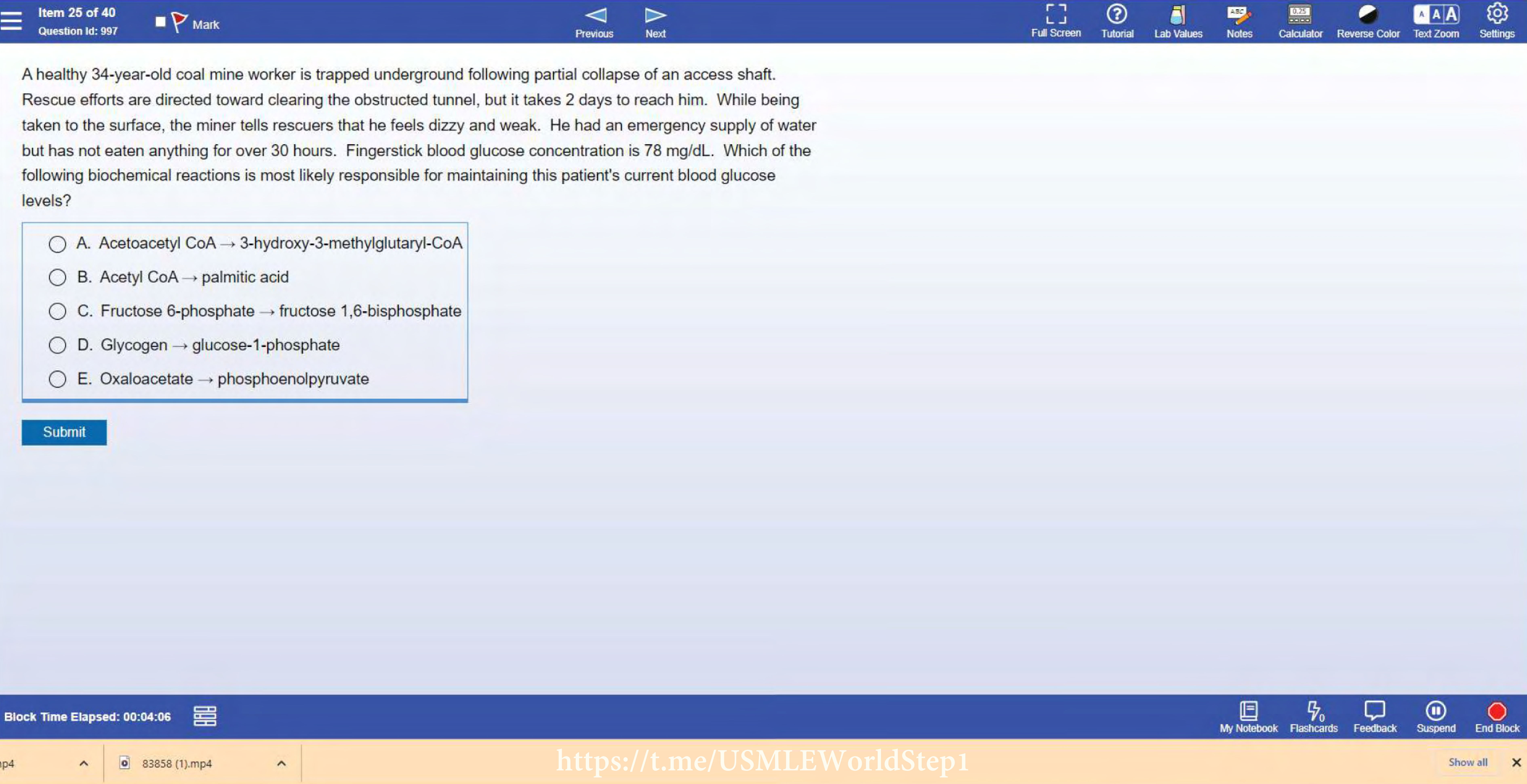
Item 25 of 40
Question Id: 997
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A healthy 34-year-old coal mine worker is trapped underground following partial collapse of an access shaft. Rescue efforts are directed toward clearing the obstructed tunnel, but it takes 2 days to reach him. While being taken to the surface, the miner tells rescuers that he feels dizzy and weak. He had an emergency supply of water but has not eaten anything for over 30 hours. Fingerstick blood glucose concentration is 78 mg/dL. Which of the following biochemical reactions is most likely responsible for maintaining this patient's current blood glucose levels?

○ A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA
○ B. Acetyl CoA → palmitic acid
○ C. Fructose 6-phosphate → fructose 1,6-bisphosphate
○ D. Glycogen → glucose-1-phosphate
○ E. Oxaloacetate → phosphoenolpyruvate

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Flashcards
Feedback
Suspend
End Block
p4
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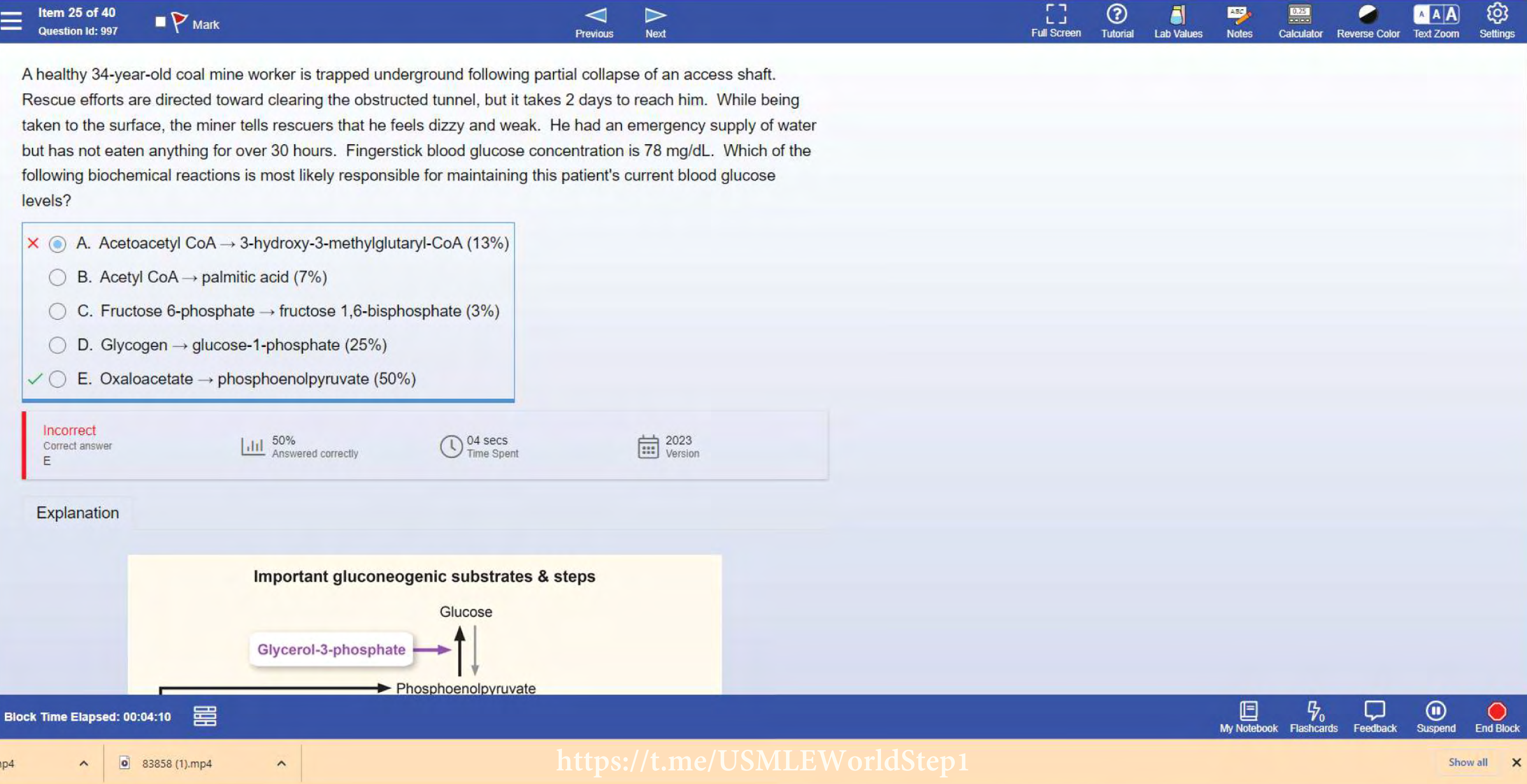
Item 25 of 40
Question Id: 997
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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✗ ● A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA (13%)
○ B. Acetyl CoA → palmitic acid (7%)
○ C. Fructose 6-phosphate → fructose 1,6-bisphosphate (3%)
○ D. Glycogen → glucose-1-phosphate (25%)
✓ ○ E. Oxaloacetate → phosphoenolpyruvate (50%)

Incorrect
Correct answer
E

50%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Important gluconeogenic substrates & steps

Glucose
Glycerol-3-phosphate
Phosphoenolpyruvate

Block Time Elapsed: 00:04:10
My Notebook
Flashcards
Feedback
Suspend
End Block

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Important gluconeogenic substrates & steps

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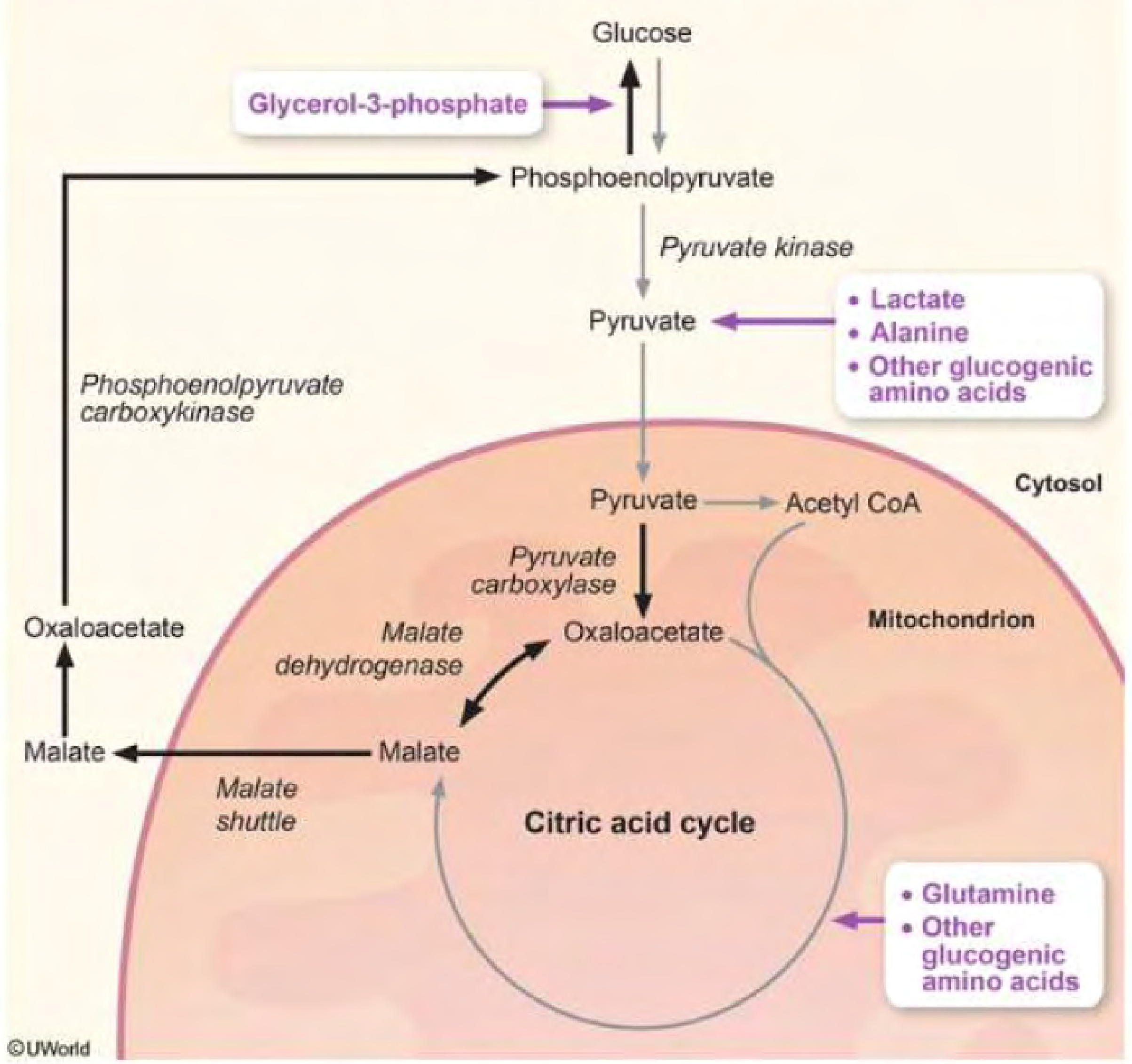
Important gluconeogenic substrates & steps


Glucose
Glycerol-3-phosphate
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
• Lactate
• Alanine
• Other glucogenic amino acids
Phosphoenolpyruvate carboxykinase
Cytosol
Pyruvate
Acetyl CoA
Pyruvate carboxylase
Mitochondrion
Oxaloacetate
Oxaloacetate
Malate dehydrogenase
Malate
Malate
Malate shuttle
Citric acid cycle
• Glutamine
• Other glucogenic amino acids
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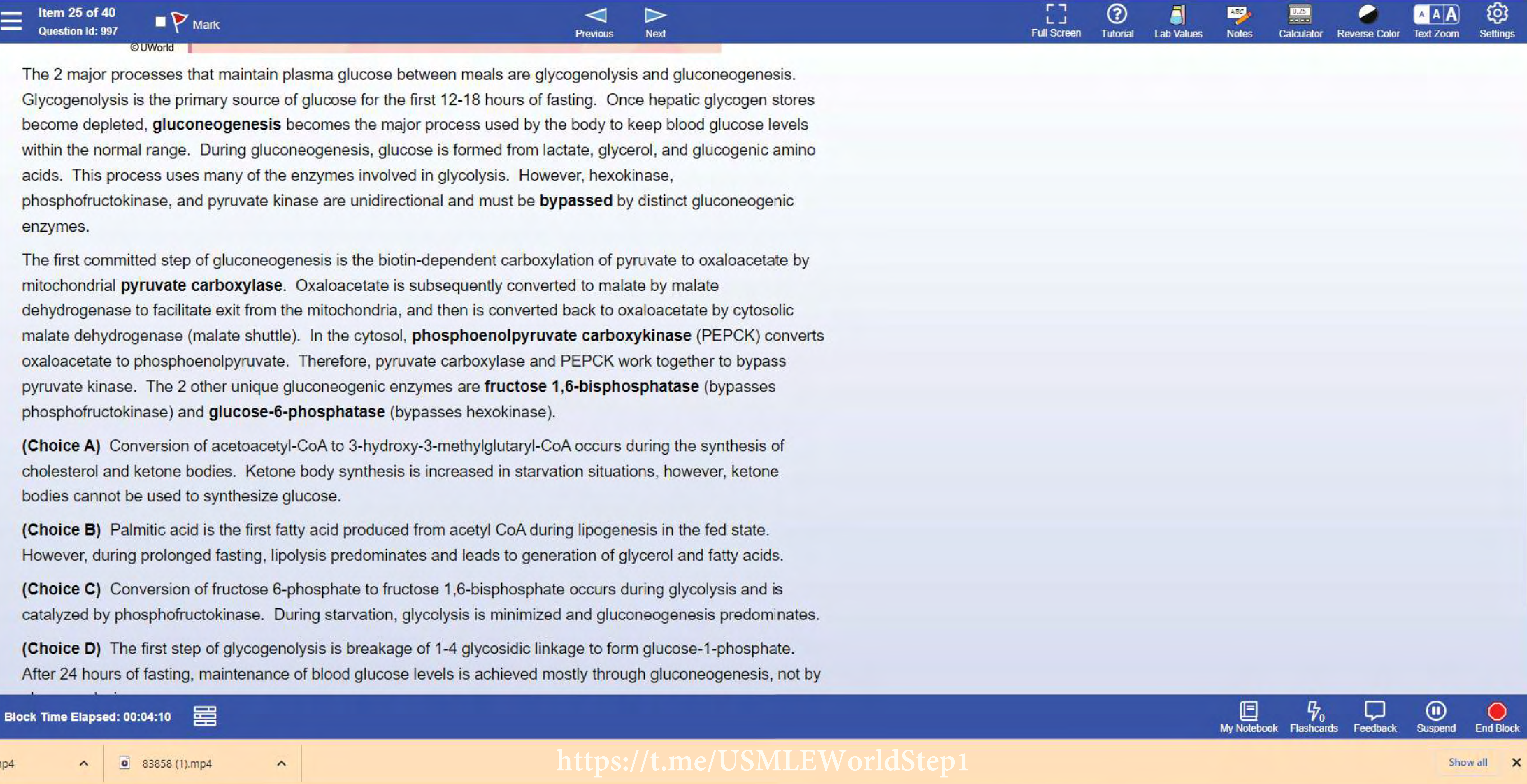
The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores



The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores become depleted, **gluconeogenesis** becomes the major process used by the body to keep blood glucose levels within the normal range. During gluconeogenesis, glucose is formed from lactate, glycerol, and glucogenic amino acids. This process uses many of the enzymes involved in glycolysis. However, hexokinase, phosphofructokinase, and pyruvate kinase are unidirectional and must be **bypassed** by distinct gluconeogenic enzymes.

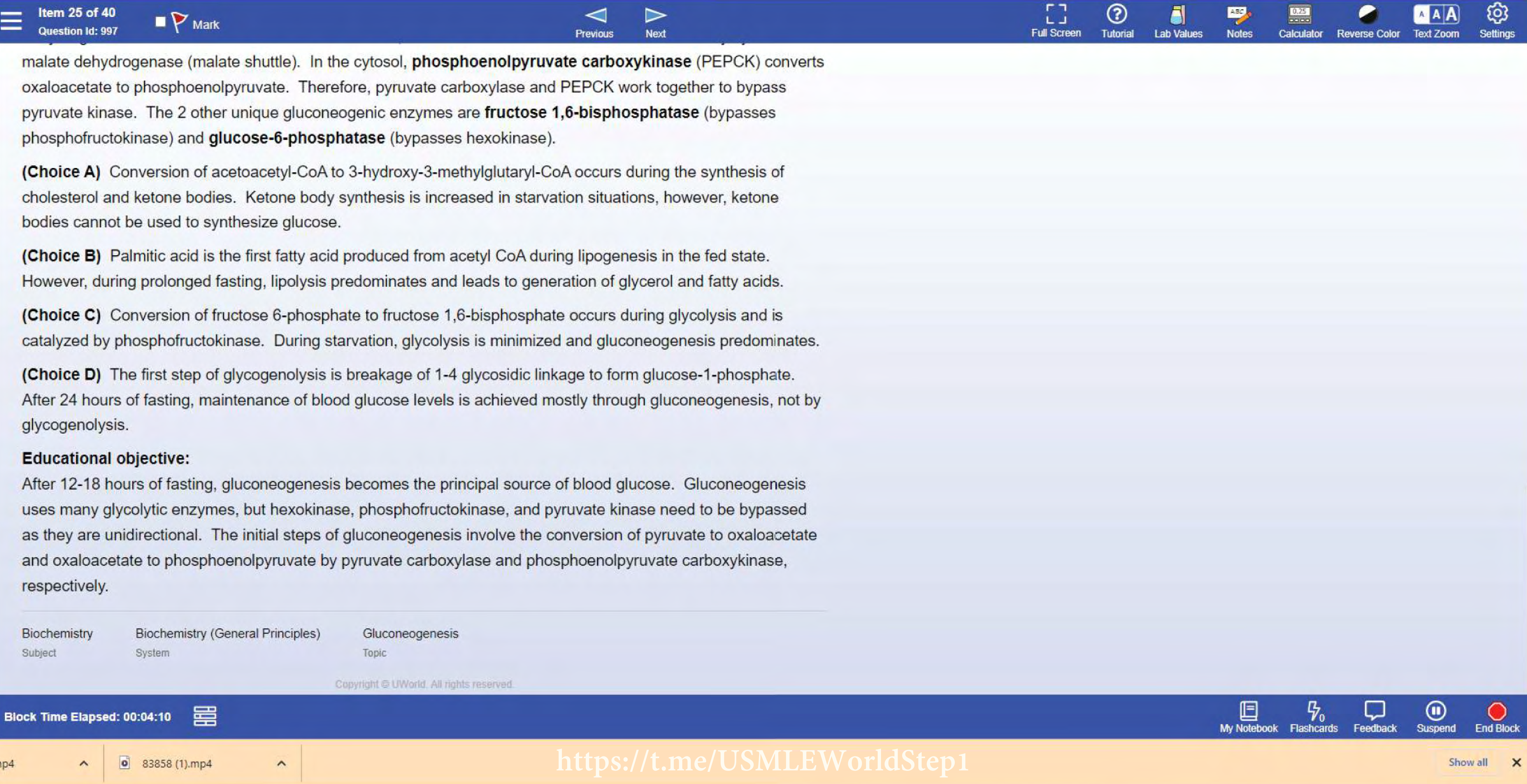
The first committed step of gluconeogenesis is the biotin-dependent carboxylation of pyruvate to oxaloacetate by mitochondrial **pyruvate carboxylase**. Oxaloacetate is subsequently converted to malate by malate dehydrogenase to facilitate exit from the mitochondria, and then is converted back to oxaloacetate by cytosolic malate dehydrogenase (malate shuttle). In the cytosol, **phosphoenolpyruvate carboxykinase** (PEPCK) converts oxaloacetate to phosphoenolpyruvate. Therefore, pyruvate carboxylase and PEPCK work together to bypass pyruvate kinase. The 2 other unique gluconeogenic enzymes are **fructose 1,6-bisphosphatase** (bypasses phosphofructokinase) and **glucose-6-phosphatase** (bypasses hexokinase).

(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however, ketone bodies cannot be used to synthesize glucose.

(Choice B) Palmitic acid is the first fatty acid produced from acetyl CoA during lipogenesis in the fed state. However, during prolonged fasting, lipolysis predominates and leads to generation of glycerol and fatty acids.

(Choice C) Conversion of fructose 6-phosphate to fructose 1,6-bisphosphate occurs during glycolysis and is catalyzed by phosphofructokinase. During starvation, glycolysis is minimized and gluconeogenesis predominates.

(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by


Item 25 of 40
Question Id: 997
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Educational objective:

After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate kinase need to be bypassed as they are unidirectional. The initial steps of gluconeogenesis involve the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate by pyruvate carboxylase and phosphoenolpyruvate carboxykinase, respectively.

Biochemistry
Subject

Biochemistry (General Principles)
System

Gluconeogenesis
Topic

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Flashcards
Feedback
Suspend
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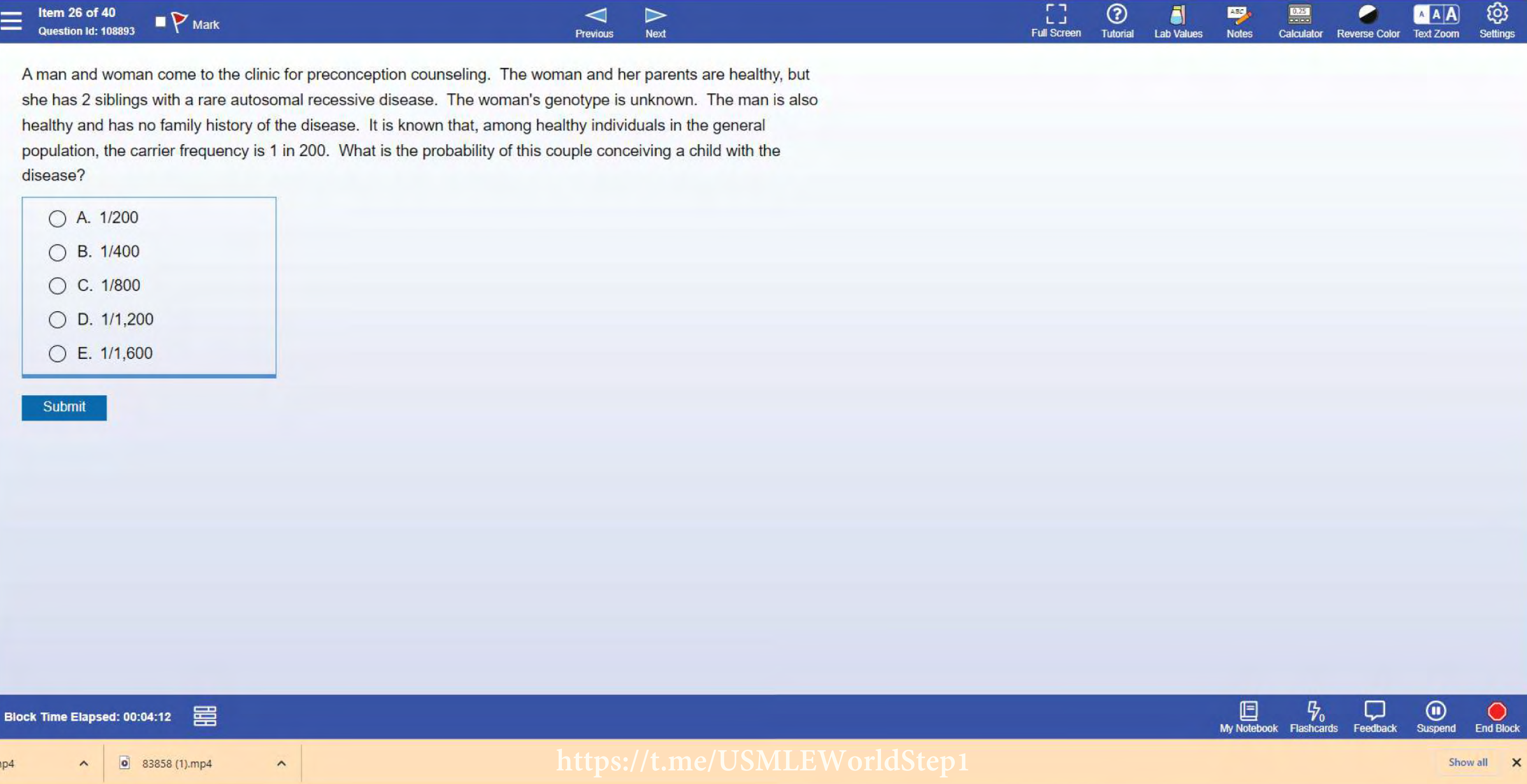
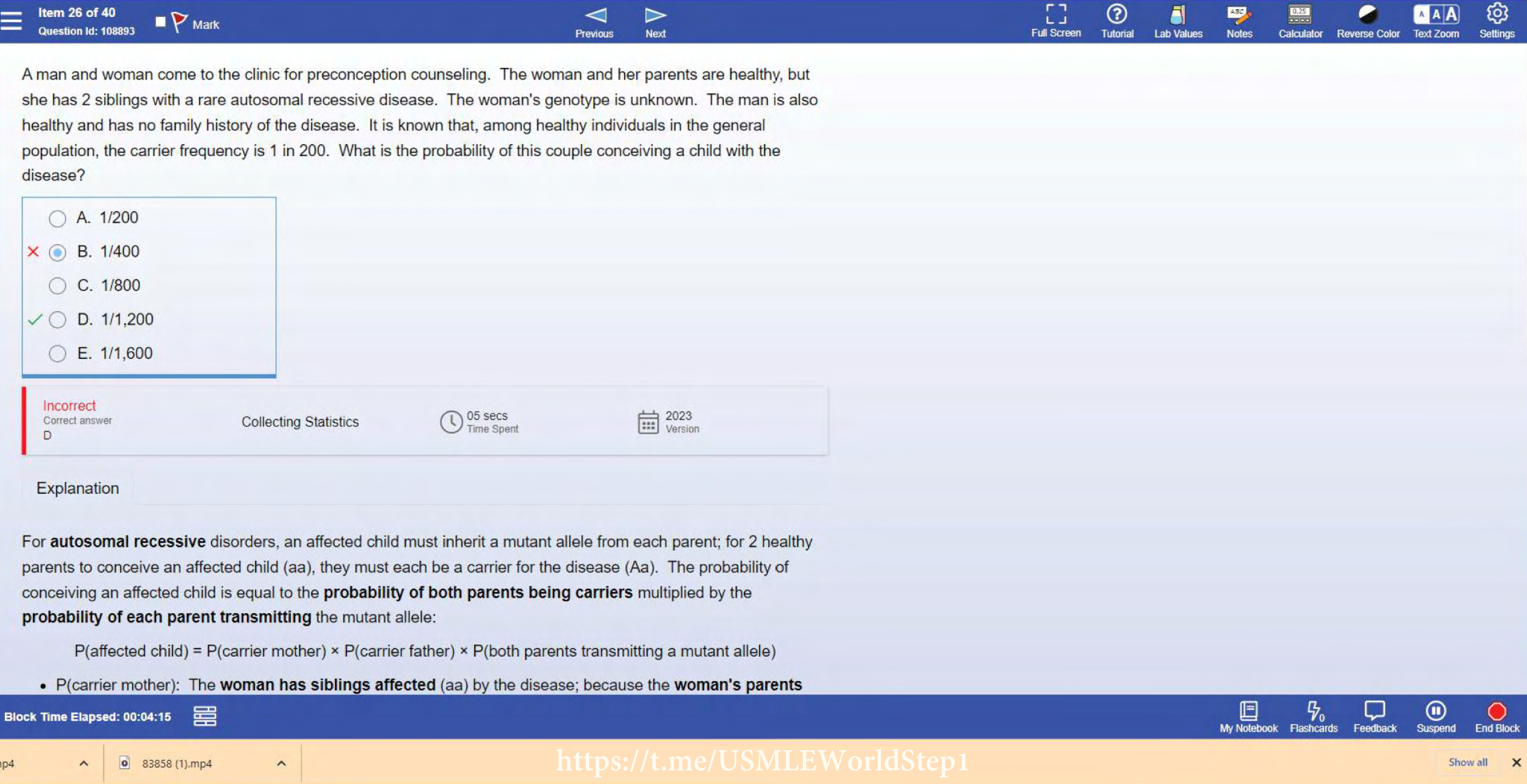


Item 26 of 40
Question Id: 108893
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A man and woman come to the clinic for preconception counseling. The woman and her parents are healthy, but she has 2 siblings with a rare autosomal recessive disease. The woman's genotype is unknown. The man is also healthy and has no family history of the disease. It is known that, among healthy individuals in the general population, the carrier frequency is 1 in 200. What is the probability of this couple conceiving a child with the disease?

- ○ A. 1/200
- ○ B. 1/400
- ○ C. 1/800
- ○ D. 1/1,200
- ○ E. 1/1,600

Submit
Block Time Elapsed: 00:04:12
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 26 of 40
Question Id: 108893
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A man and woman come to the clinic for preconception counseling. The woman and her parents are healthy, but she has 2 siblings with a rare autosomal recessive disease. The woman's genotype is unknown. The man is also healthy and has no family history of the disease. It is known that, among healthy individuals in the general population, the carrier frequency is 1 in 200. What is the probability of this couple conceiving a child with the disease?

○ A. 1/200

✗ ● B. 1/400

○ C. 1/800

✓ ○ D. 1/1,200

○ E. 1/1,600

Incorrect
Correct answer
D

Collecting Statistics

05 secs
Time Spent

2023
Version

Explanation

For **autosomal recessive** disorders, an affected child must inherit a mutant allele from each parent; for 2 healthy parents to conceive an affected child (aa), they must each be a carrier for the disease (Aa). The probability of conceiving an affected child is equal to the **probability of both parents being carriers** multiplied by the **probability of each parent transmitting** the mutant allele:

P(affected child) = P(carrier mother) × P(carrier father) × P(both parents transmitting a mutant allele)

- P(carrier mother): The **woman has siblings affected** (aa) by the disease; because the **woman's parents**

Block Time Elapsed: 00:04:15
My Notebook
Flashcards
Feedback
Suspend
End Block
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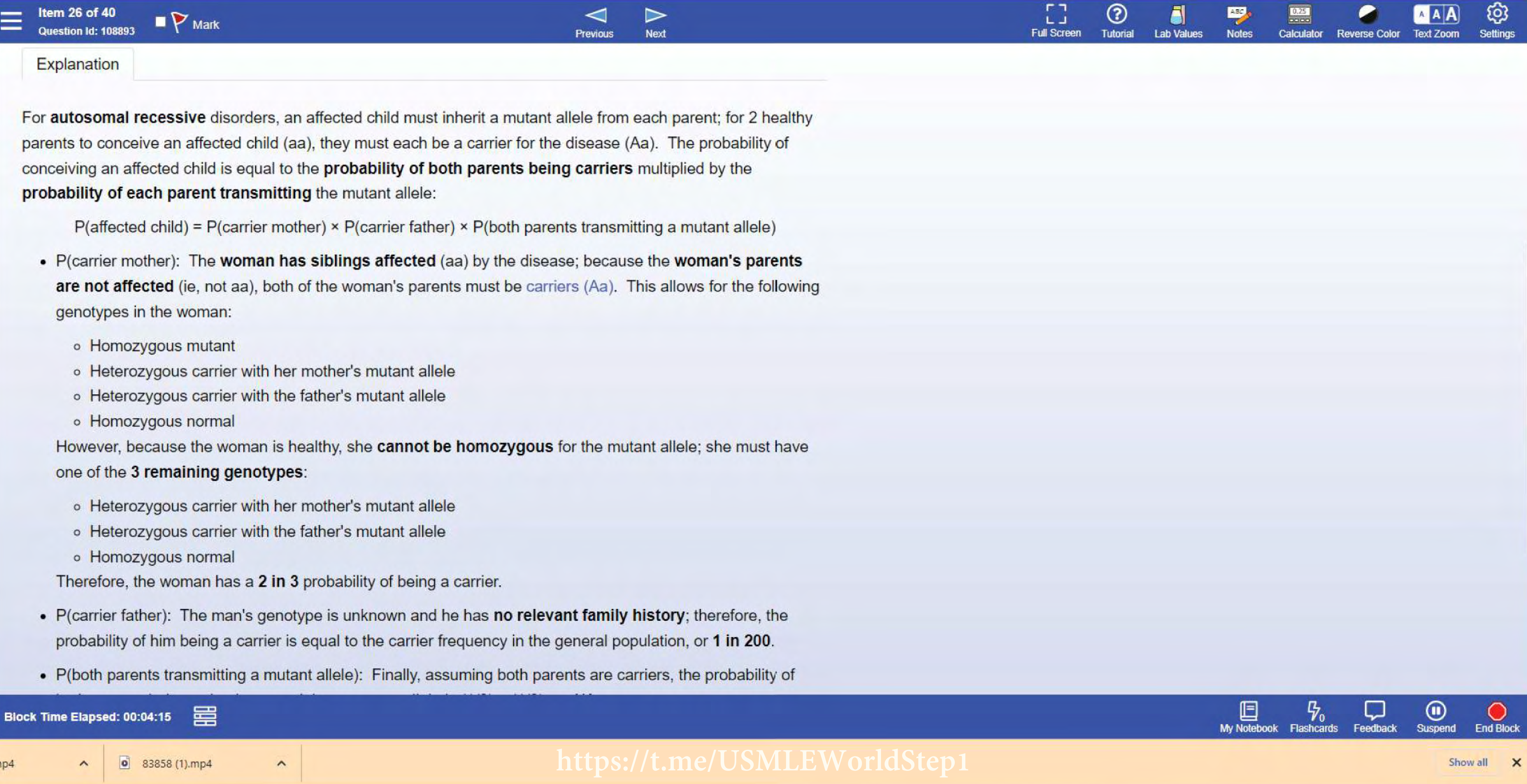
Show all


Item 26 of 40
Question Id: 108893
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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P(affected child) = P(carrier mother) × P(carrier father) × P(both parents transmitting a mutant allele)

- P(carrier mother): The **woman has siblings affected** (aa) by the disease; because the **woman's parents are not affected** (ie, not aa), both of the woman's parents must be carriers (Aa). This allows for the following genotypes in the woman:
    - Homozygous mutant
    - Heterozygous carrier with her mother's mutant allele
    - Heterozygous carrier with the father's mutant allele
    - Homozygous normal

  However, because the woman is healthy, she **cannot be homozygous** for the mutant allele; she must have one of the **3 remaining genotypes**:
    - Heterozygous carrier with her mother's mutant allele
    - Heterozygous carrier with the father's mutant allele
    - Homozygous normal

  Therefore, the woman has a **2 in 3** probability of being a carrier.
- P(carrier father): The man's genotype is unknown and he has **no relevant family history**; therefore, the probability of him being a carrier is equal to the carrier frequency in the general population, or **1 in 200**.
- P(both parents transmitting a mutant allele): Finally, assuming both parents are carriers, the probability of

Block Time Elapsed: 00:04:15
My Notebook
Flashcards
Feedback
Suspend
End Block
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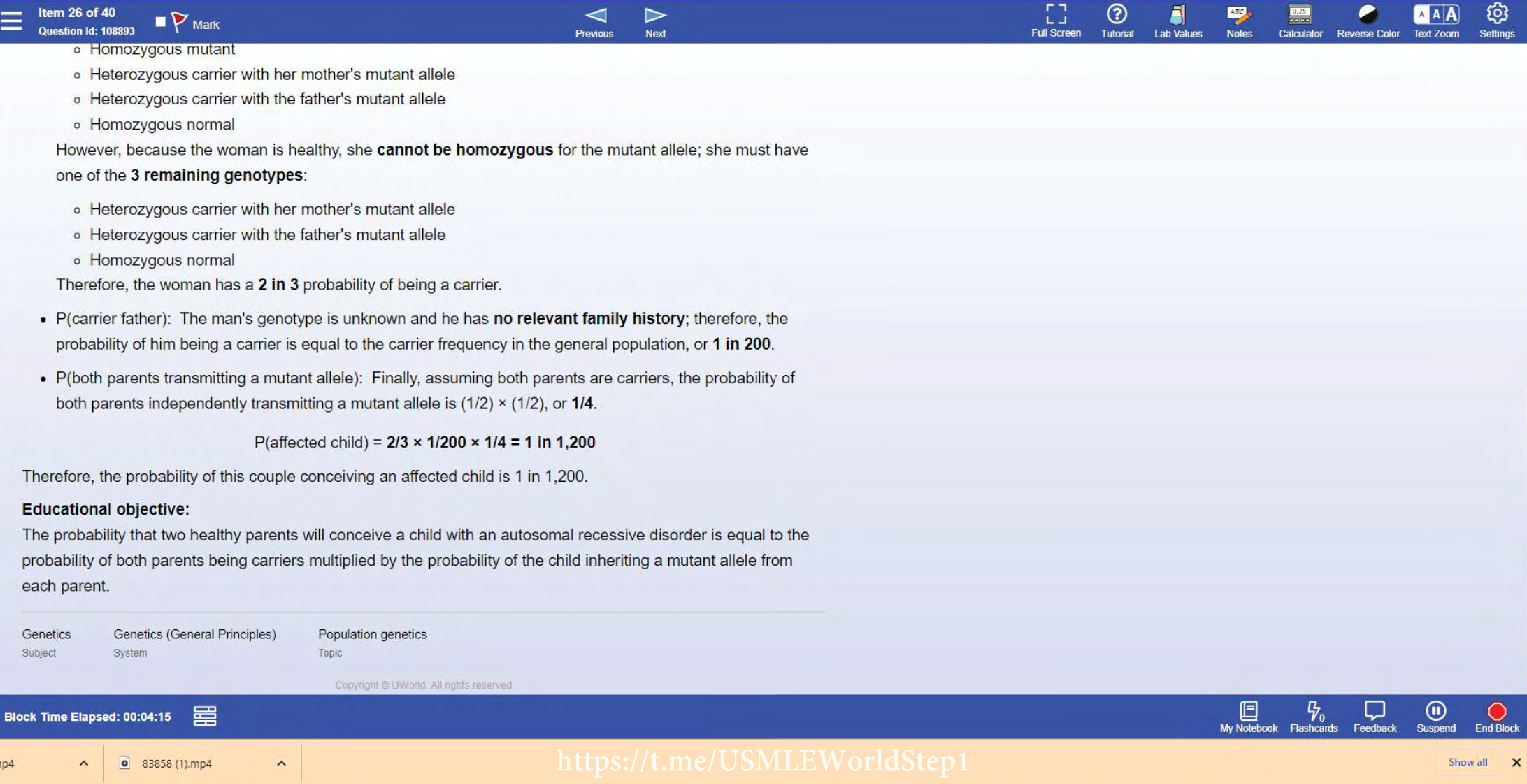
Item 26 of 40
Question Id: 108893
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

  - Homozygous mutant
  - Heterozygous carrier with her mother's mutant allele
  - Heterozygous carrier with the father's mutant allele
  - Homozygous normal

  However, because the woman is healthy, she **cannot be homozygous** for the mutant allele; she must have one of the **3 remaining genotypes**:

  - Heterozygous carrier with her mother's mutant allele
  - Heterozygous carrier with the father's mutant allele
  - Homozygous normal

  Therefore, the woman has a **2 in 3** probability of being a carrier.

- P(carrier father): The man's genotype is unknown and he has **no relevant family history**; therefore, the probability of him being a carrier is equal to the carrier frequency in the general population, or **1 in 200**.
- P(both parents transmitting a mutant allele): Finally, assuming both parents are carriers, the probability of both parents independently transmitting a mutant allele is (1/2) × (1/2), or **1/4**.

P(affected child) = **2/3 × 1/200 × 1/4 = 1 in 1,200**

Therefore, the probability of this couple conceiving an affected child is 1 in 1,200.

Educational objective:

The probability that two healthy parents will conceive a child with an autosomal recessive disorder is equal to the probability of both parents being carriers multiplied by the probability of the child inheriting a mutant allele from each parent.

Genetics	Genetics (General Principles)	Population genetics
Subject	System	Topic

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Feedback
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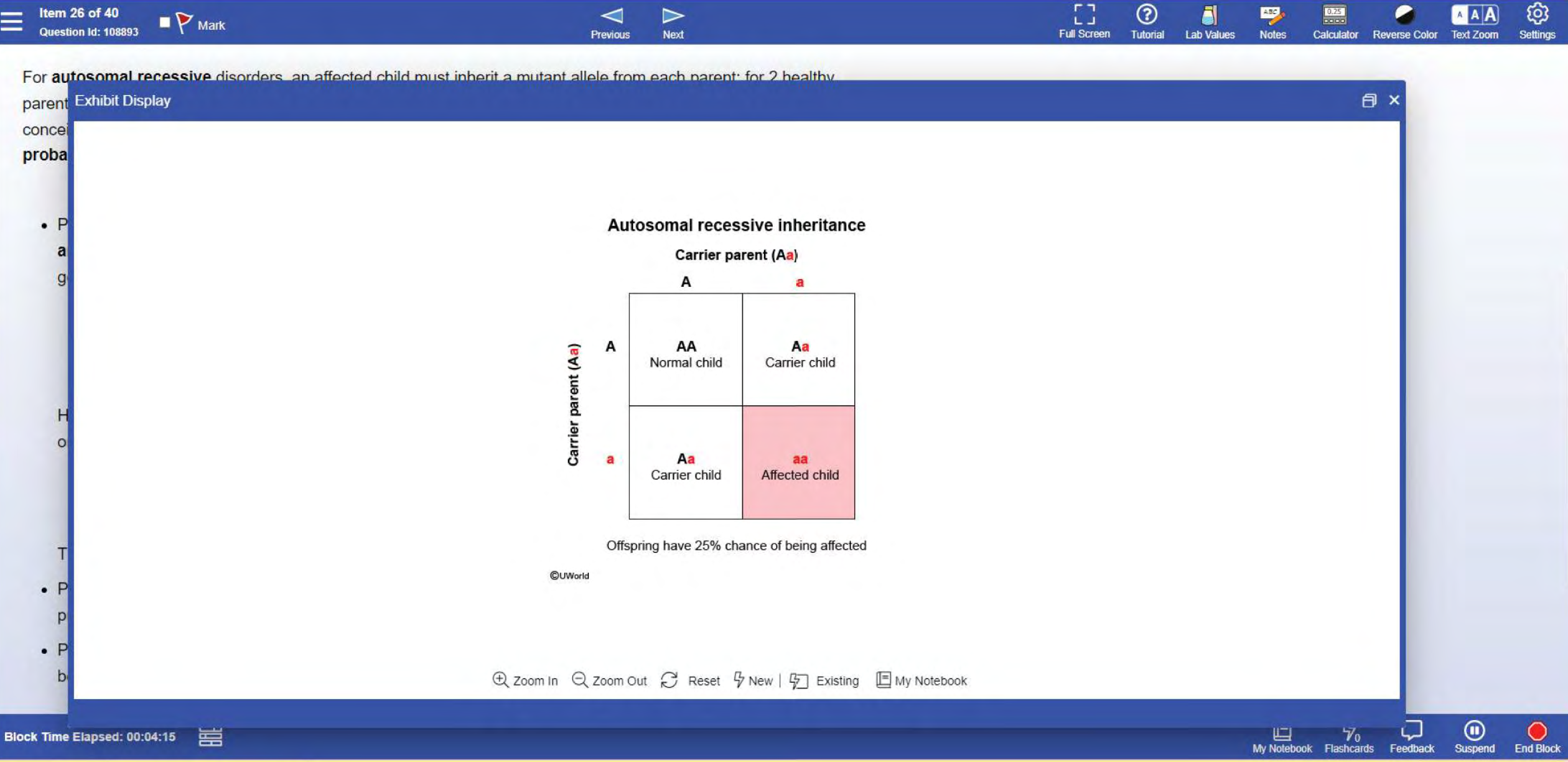
Item 26 of 40
Question Id: 108893
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:04:15
My Notebook
Flashcards
Feedback
Suspend
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For **autosomal recessive** disorders, an affected child must inherit a mutant allele from each parent; for 2 healthy

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Autosomal recessive inheritance

Carrier parent (Aa)

		A	**a**
Carrier parent (Aa)	**A**	**AA** Normal child	**Aa** Carrier child
	a	**Aa** Carrier child	**aa** Affected child

Offspring have 25% chance of being affected

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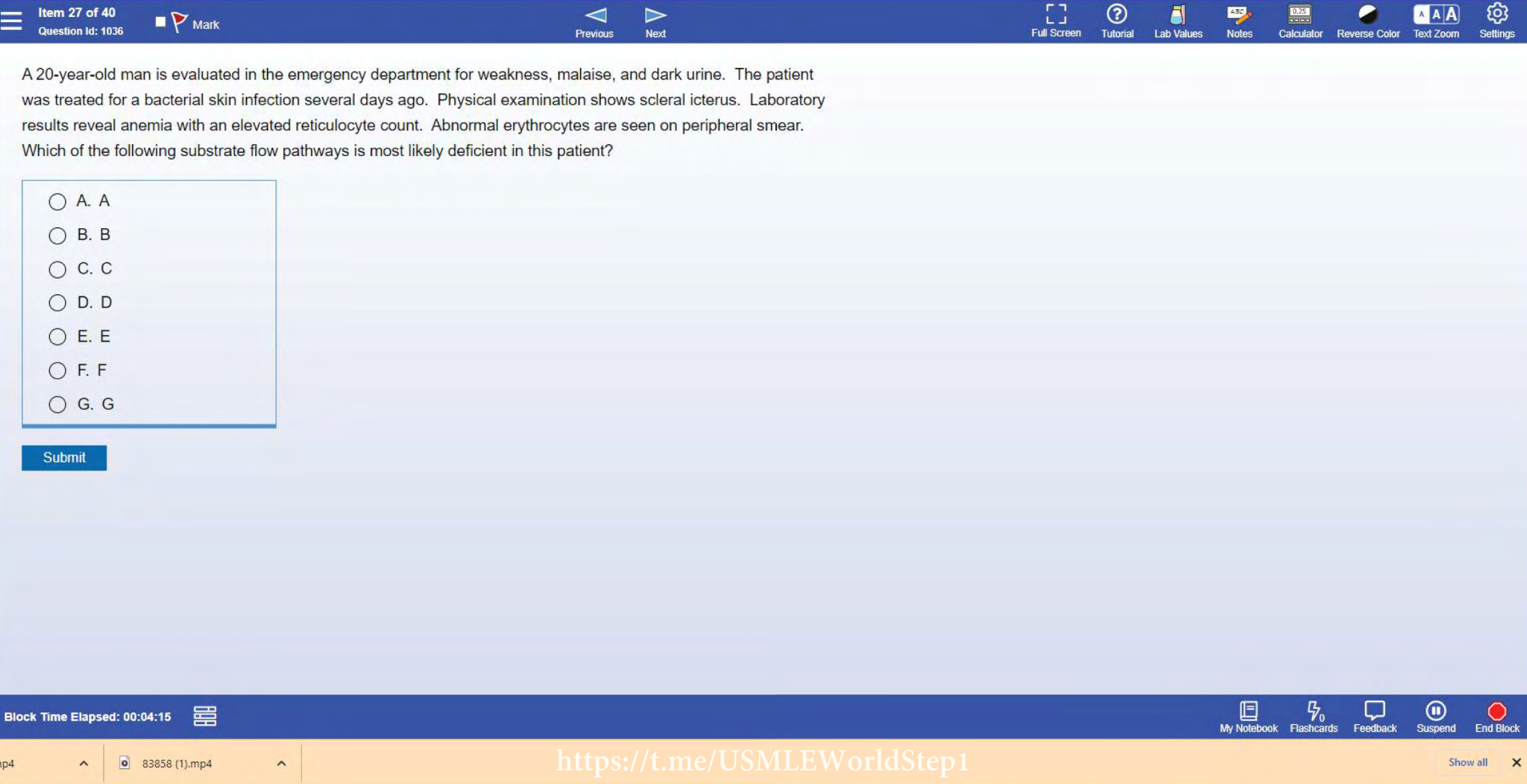
Item 27 of 40
Question Id: 1036
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 20-year-old man is evaluated in the emergency department for weakness, malaise, and dark urine. The patient was treated for a bacterial skin infection several days ago. Physical examination shows scleral icterus. Laboratory results reveal anemia with an elevated reticulocyte count. Abnormal erythrocytes are seen on peripheral smear. Which of the following substrate flow pathways is most likely deficient in this patient?

○ A. A
○ B. B
○ C. C
○ D. D
○ E. E
○ F. F
○ G. G

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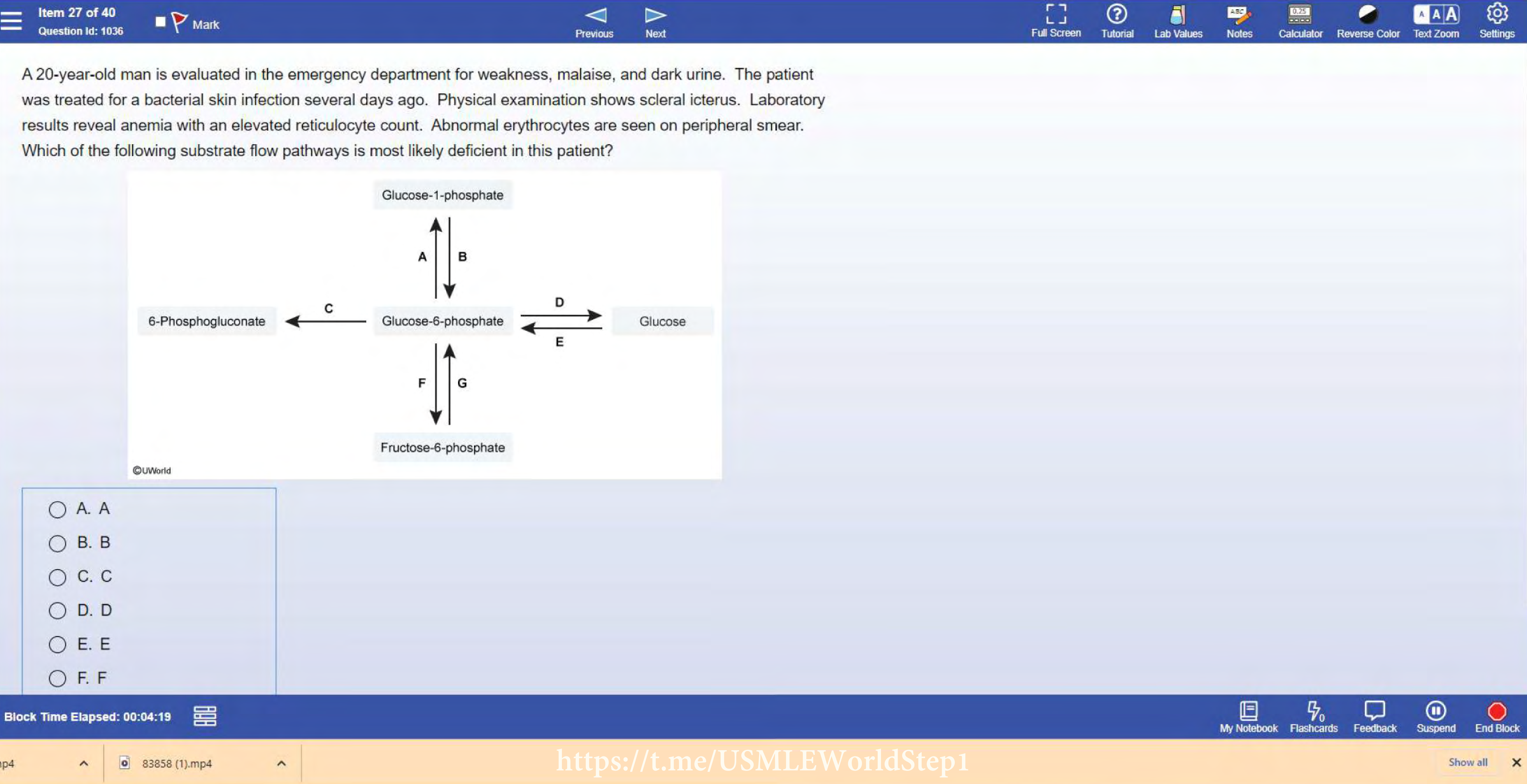

Item 27 of 40
Question Id: 1036
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Glucose-1-phosphate
A
B
6-Phosphogluconate
C
Glucose-6-phosphate
D
E
Glucose
F
G
Fructose-6-phosphate

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○ A. A

○ B. B

○ C. C

○ D. D

○ E. E

○ F. F

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Flashcards
Feedback
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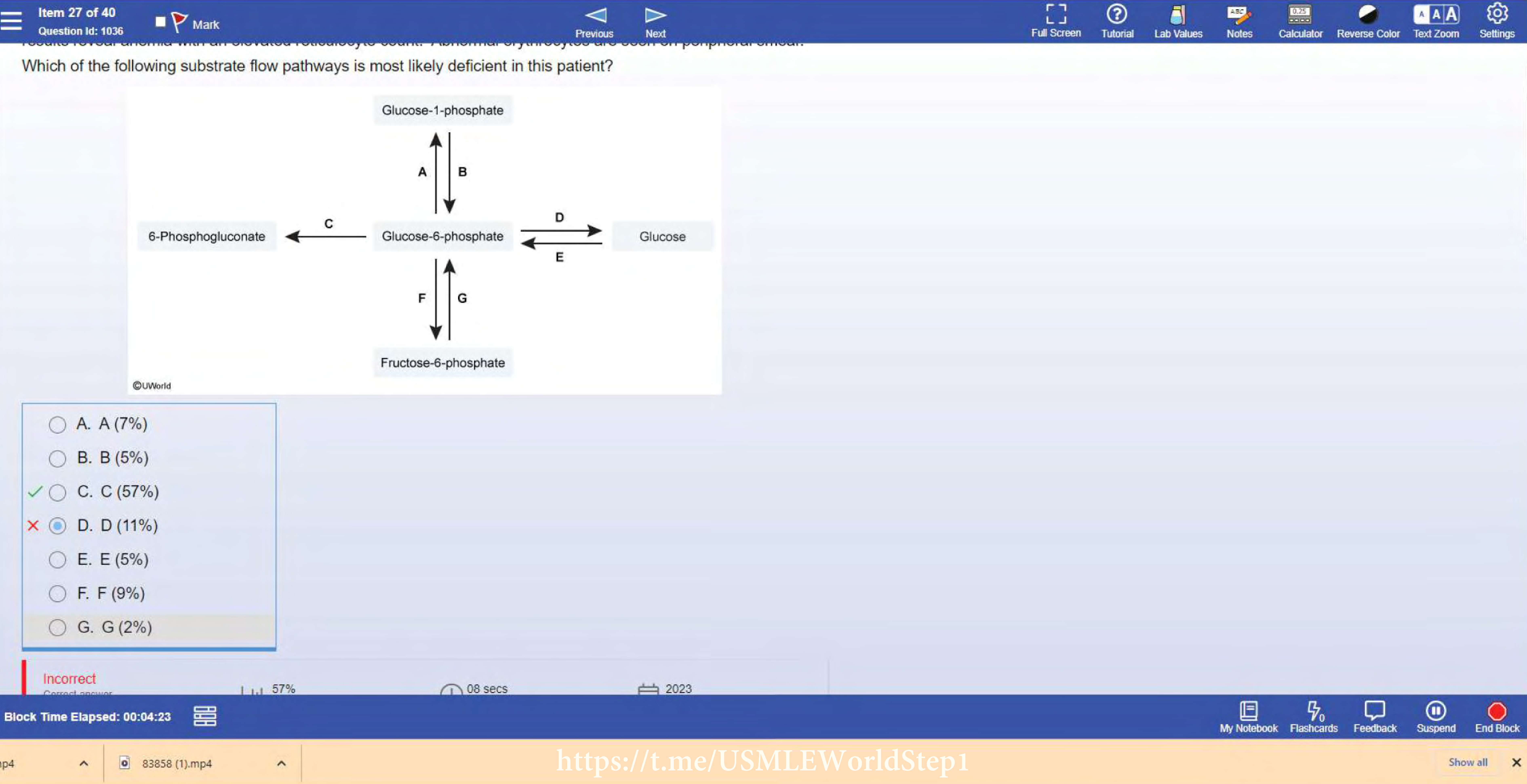

Item 27 of 40
Question Id: 1036
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Glucose-1-phosphate
A
B
6-Phosphogluconate
C
Glucose-6-phosphate
D
E
Glucose
F
G
Fructose-6-phosphate
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My Notebook
Flashcards
Feedback
Suspend
End Block
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results reveal anemia with an elevated reticulocyte count. Abnormal erythrocytes are seen on peripheral smear.

Which of the following substrate flow pathways is most likely deficient in this patient?

○ A. A (7%)

○ B. B (5%)

✓ ○ C. C (57%)

✗ ● D. D (11%)

○ E. E (5%)

○ F. F (9%)

○ G. G (2%)

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57%

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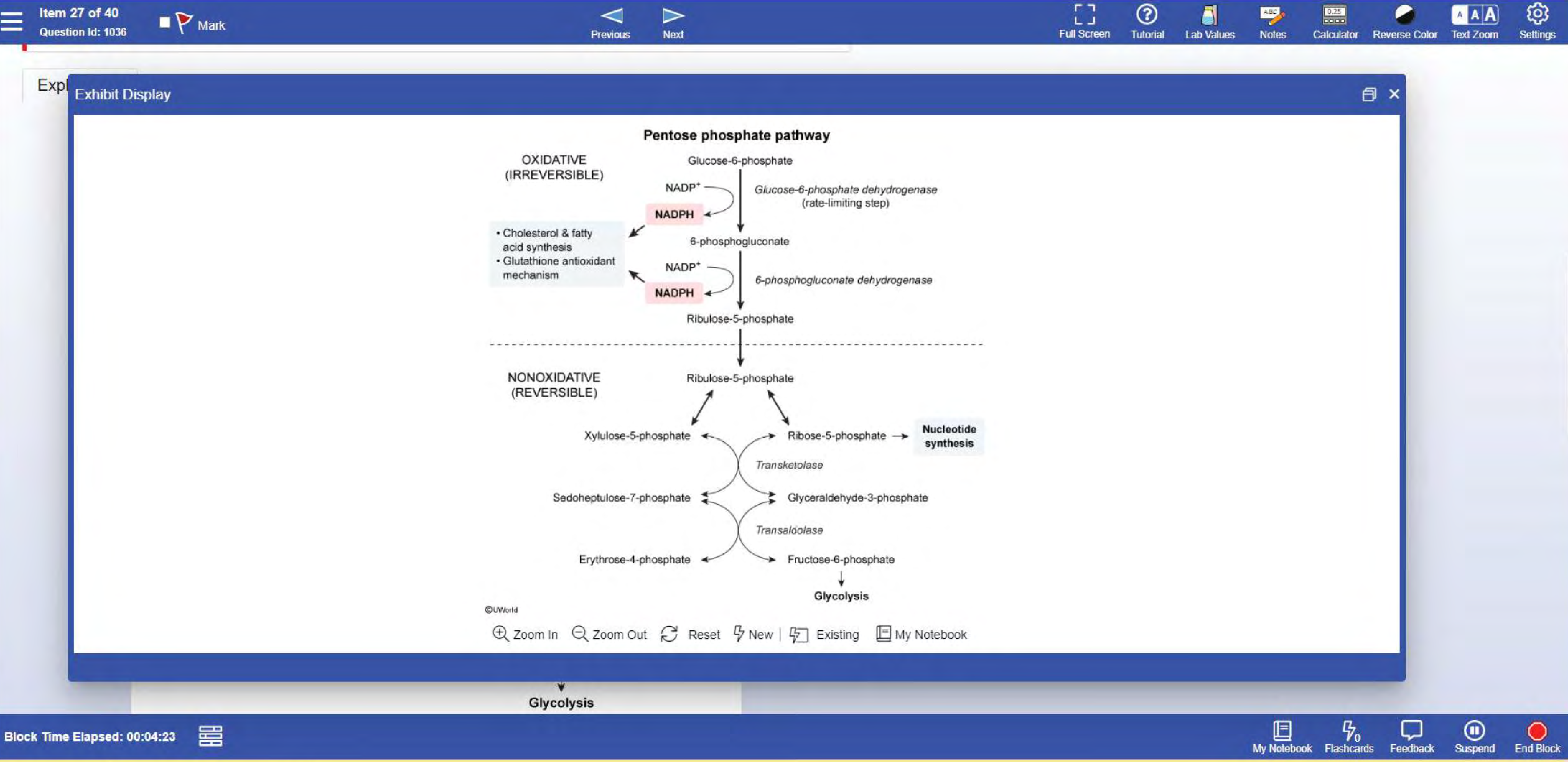

Item 27 of 40
Question Id: 1036

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Pentose phosphate pathway
OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP⁺
NADPH
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
• Cholesterol & fatty acid synthesis
• Glutathione antioxidant mechanism
6-phosphogluconate
NADP⁺
NADPH
6-phosphogluconate dehydrogenase
Ribulose-5-phosphate
NONOXIDATIVE
(REVERSIBLE)
Ribulose-5-phosphate
Xylulose-5-phosphate
Ribose-5-phosphate
Nucleotide synthesis
Transketolase
Sedoheptulose-7-phosphate
Glyceraldehyde-3-phosphate
Transaldolase
Erythrose-4-phosphate
Fructose-6-phosphate
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Zoom In
Zoom Out
Reset
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Flashcards
Feedback
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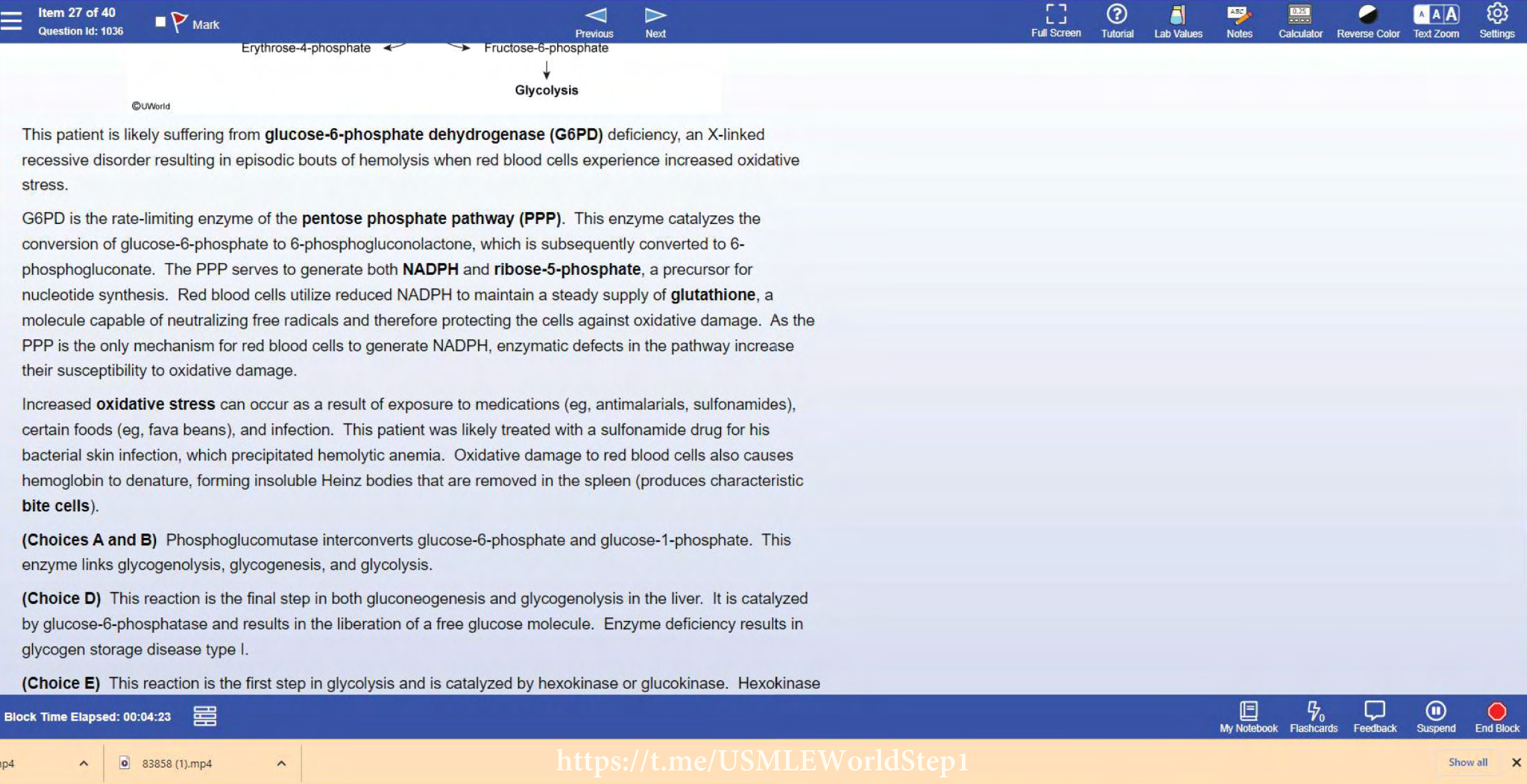
Item 27 of 40
Question Id: 1036
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Fructose-6-phosphate
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©UWorld
Block Time Elapsed: 00:04:23
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

This patient is likely suffering from **glucose-6-phosphate dehydrogenase (G6PD)** deficiency, an X-linked recessive disorder resulting in episodic bouts of hemolysis when red blood cells experience increased oxidative stress.

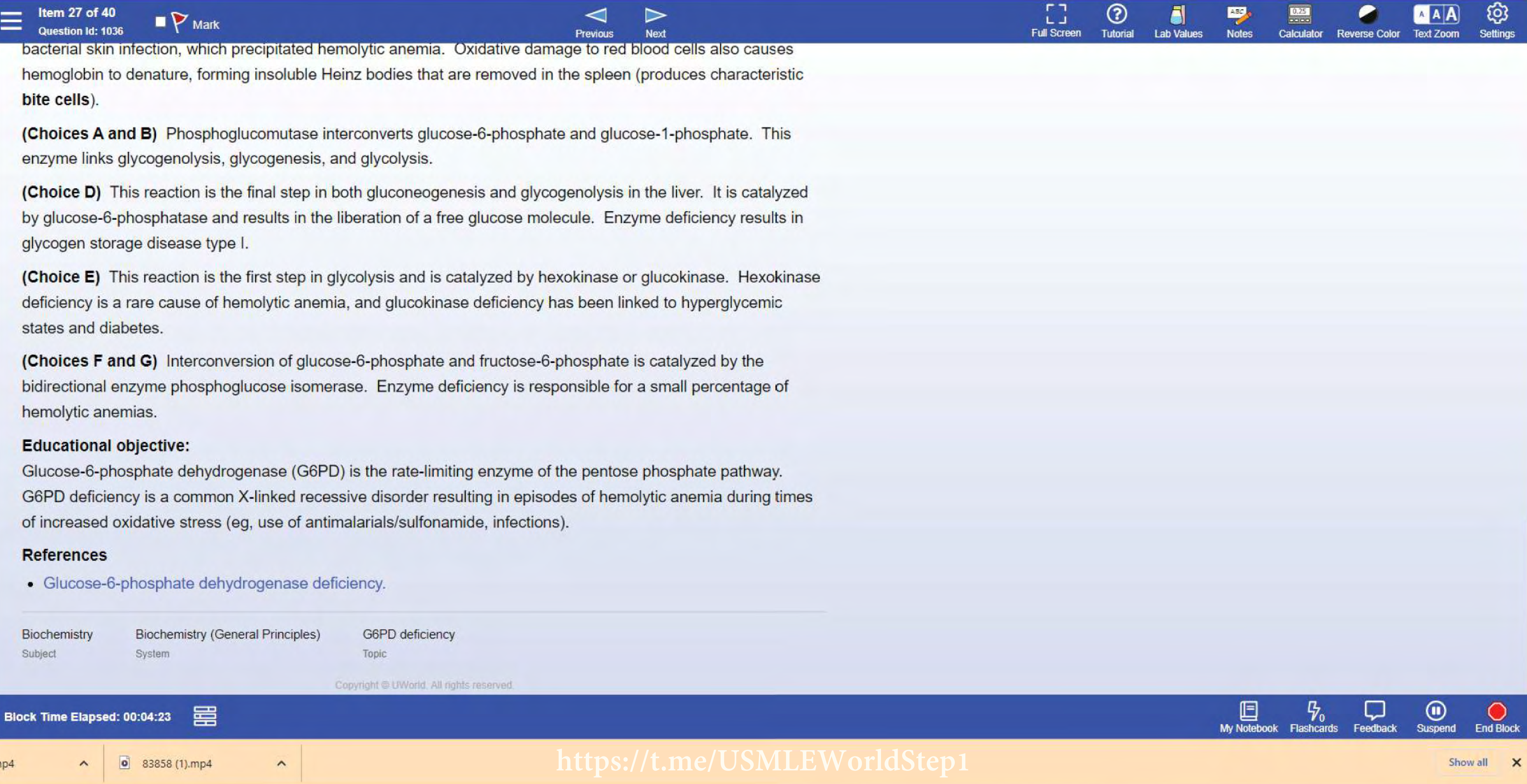
G6PD is the rate-limiting enzyme of the **pentose phosphate pathway (PPP)**. This enzyme catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone, which is subsequently converted to 6-phosphogluconate. The PPP serves to generate both **NADPH** and **ribose-5-phosphate**, a precursor for nucleotide synthesis. Red blood cells utilize reduced NADPH to maintain a steady supply of **glutathione**, a molecule capable of neutralizing free radicals and therefore protecting the cells against oxidative damage. As the PPP is the only mechanism for red blood cells to generate NADPH, enzymatic defects in the pathway increase their susceptibility to oxidative damage.

Increased **oxidative stress** can occur as a result of exposure to medications (eg, antimalarials, sulfonamides), certain foods (eg, fava beans), and infection. This patient was likely treated with a sulfonamide drug for his bacterial skin infection, which precipitated hemolytic anemia. Oxidative damage to red blood cells also causes hemoglobin to denature, forming insoluble Heinz bodies that are removed in the spleen (produces characteristic **bite cells**).

(Choices A and B) Phosphoglucomutase interconverts glucose-6-phosphate and glucose-1-phosphate. This enzyme links glycogenolysis, glycogenesis, and glycolysis.

(Choice D) This reaction is the final step in both gluconeogenesis and glycogenolysis in the liver. It is catalyzed by glucose-6-phosphatase and results in the liberation of a free glucose molecule. Enzyme deficiency results in glycogen storage disease type I.

(Choice E) This reaction is the first step in glycolysis and is catalyzed by hexokinase or glucokinase. Hexokinase


Item 27 of 40
Question Id: 1036
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:23
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

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(Choice D) This reaction is the final step in both gluconeogenesis and glycogenolysis in the liver. It is catalyzed by glucose-6-phosphatase and results in the liberation of a free glucose molecule. Enzyme deficiency results in glycogen storage disease type I.

(Choice E) This reaction is the first step in glycolysis and is catalyzed by hexokinase or glucokinase. Hexokinase deficiency is a rare cause of hemolytic anemia, and glucokinase deficiency has been linked to hyperglycemic states and diabetes.

(Choices F and G) Interconversion of glucose-6-phosphate and fructose-6-phosphate is catalyzed by the bidirectional enzyme phosphoglucose isomerase. Enzyme deficiency is responsible for a small percentage of hemolytic anemias.

Educational objective:

Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the pentose phosphate pathway. G6PD deficiency is a common X-linked recessive disorder resulting in episodes of hemolytic anemia during times of increased oxidative stress (eg, use of antimalarials/sulfonamide, infections).

References

- Glucose-6-phosphate dehydrogenase deficiency.

Biochemistry	Biochemistry (General Principles)	G6PD deficiency
Subject	System	Topic

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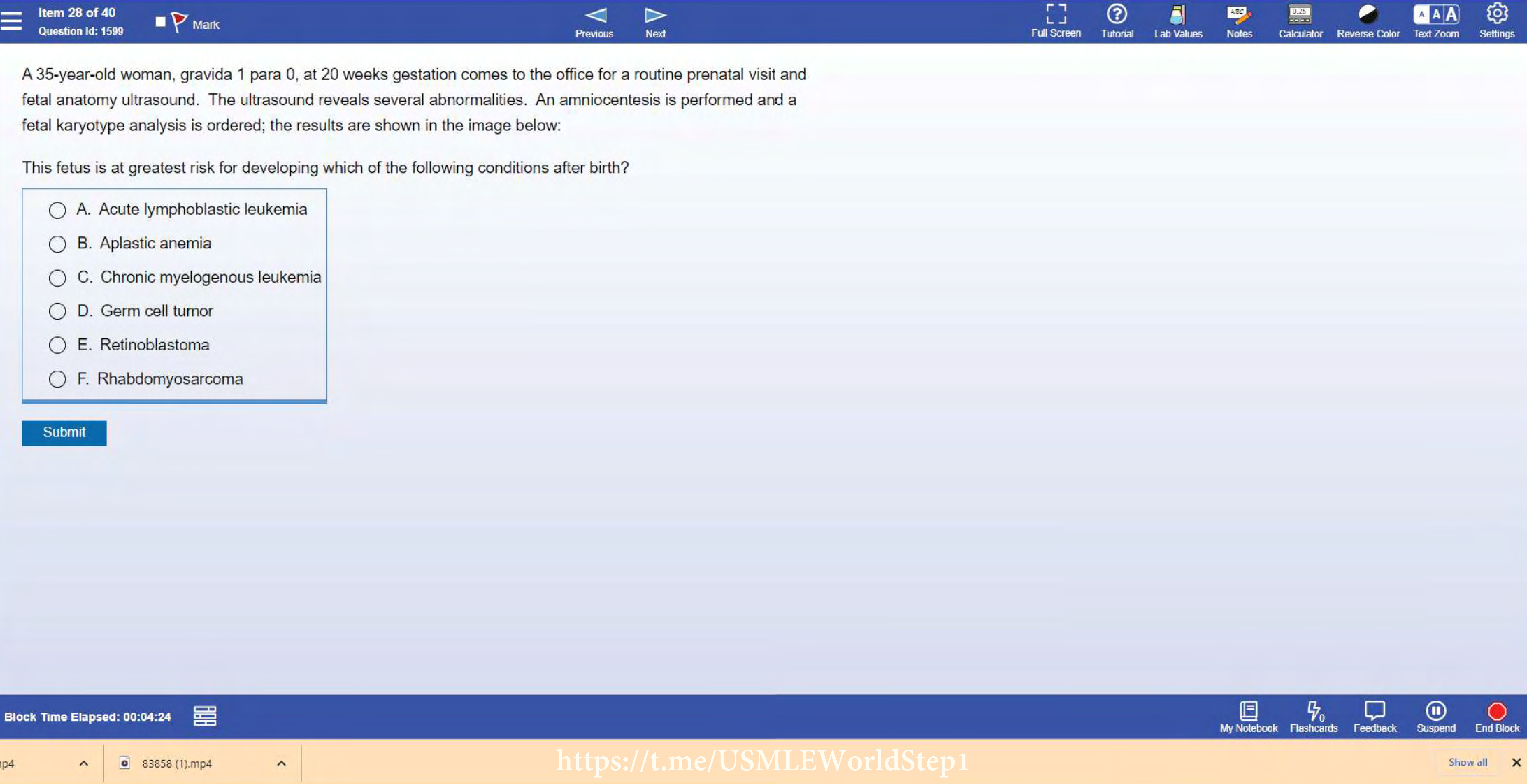
Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 35-year-old woman, gravida 1 para 0, at 20 weeks gestation comes to the office for a routine prenatal visit and fetal anatomy ultrasound. The ultrasound reveals several abnormalities. An amniocentesis is performed and a fetal karyotype analysis is ordered; the results are shown in the image below:

This fetus is at greatest risk for developing which of the following conditions after birth?

- ○ A. Acute lymphoblastic leukemia
- ○ B. Aplastic anemia
- ○ C. Chronic myelogenous leukemia
- ○ D. Germ cell tumor
- ○ E. Retinoblastoma
- ○ F. Rhabdomyosarcoma

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Feedback
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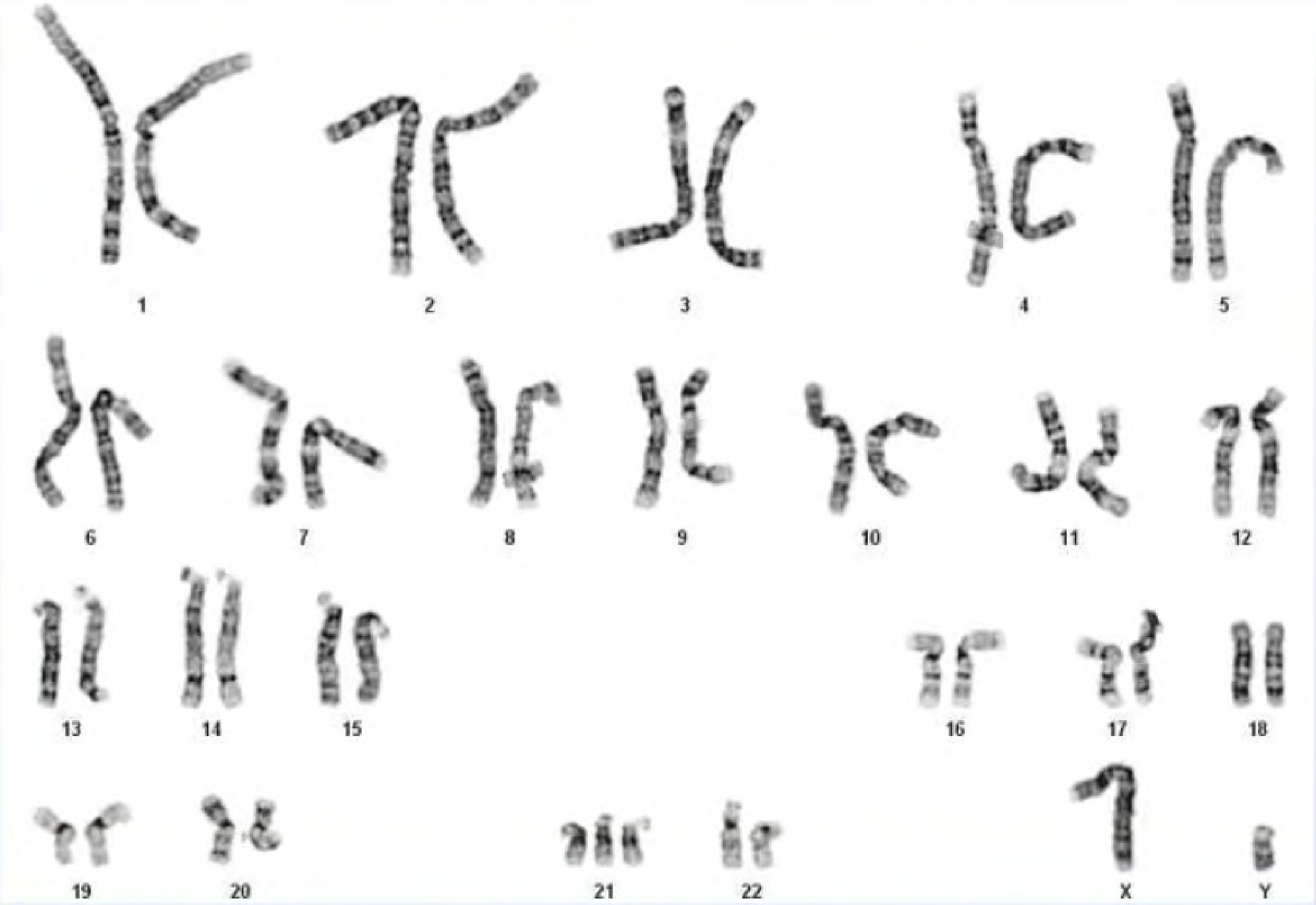

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○ B. Aplastic anemia
○ C. Chronic myelogenous leukemia

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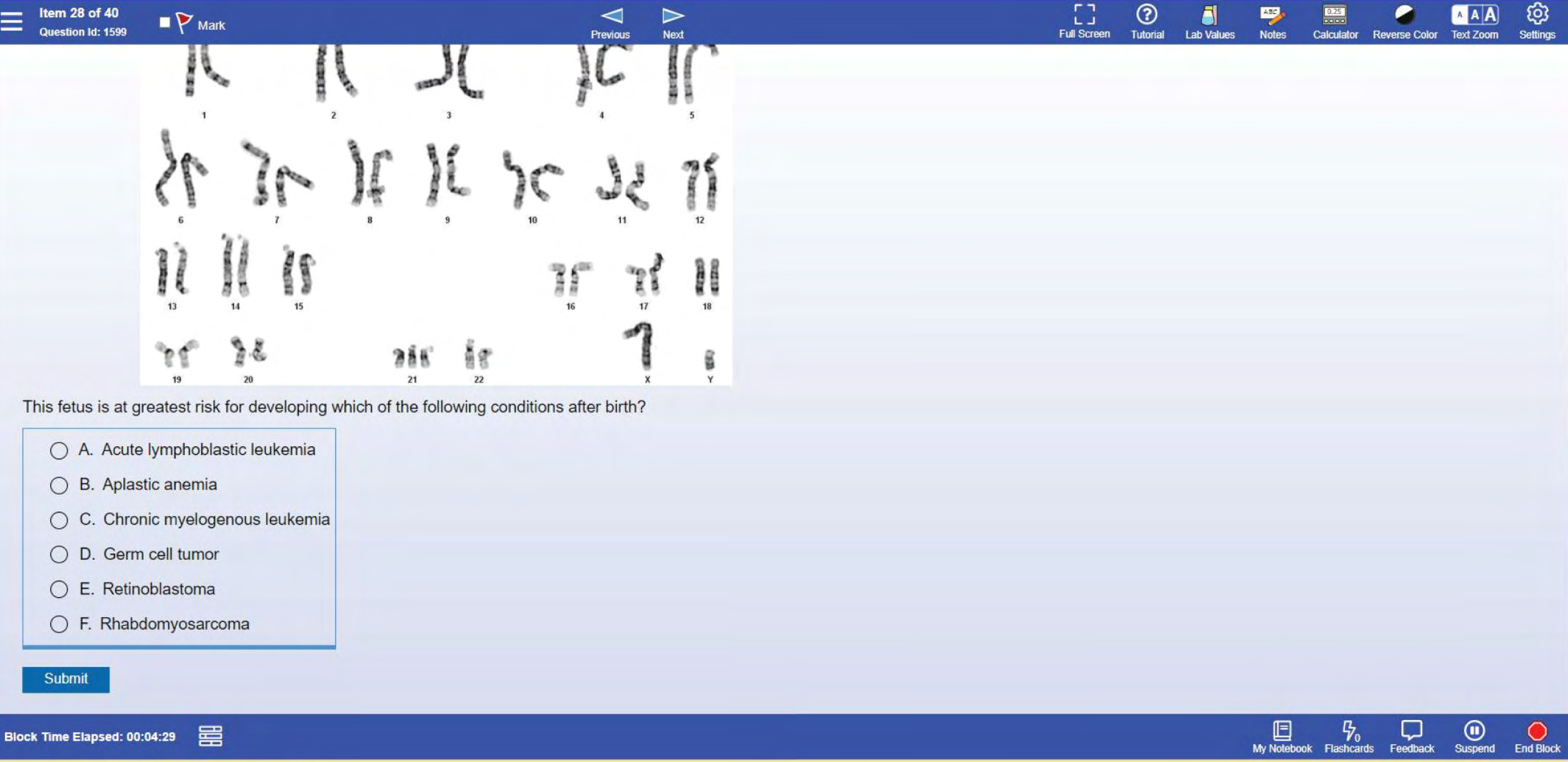
Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
1
2
3
4
5
6
7
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This fetus is at greatest risk for developing which of the following conditions after birth?

○ A. Acute lymphoblastic leukemia
○ B. Aplastic anemia
○ C. Chronic myelogenous leukemia
○ D. Germ cell tumor
○ E. Retinoblastoma
○ F. Rhabdomyosarcoma

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My Notebook
Flashcards
Feedback
Suspend
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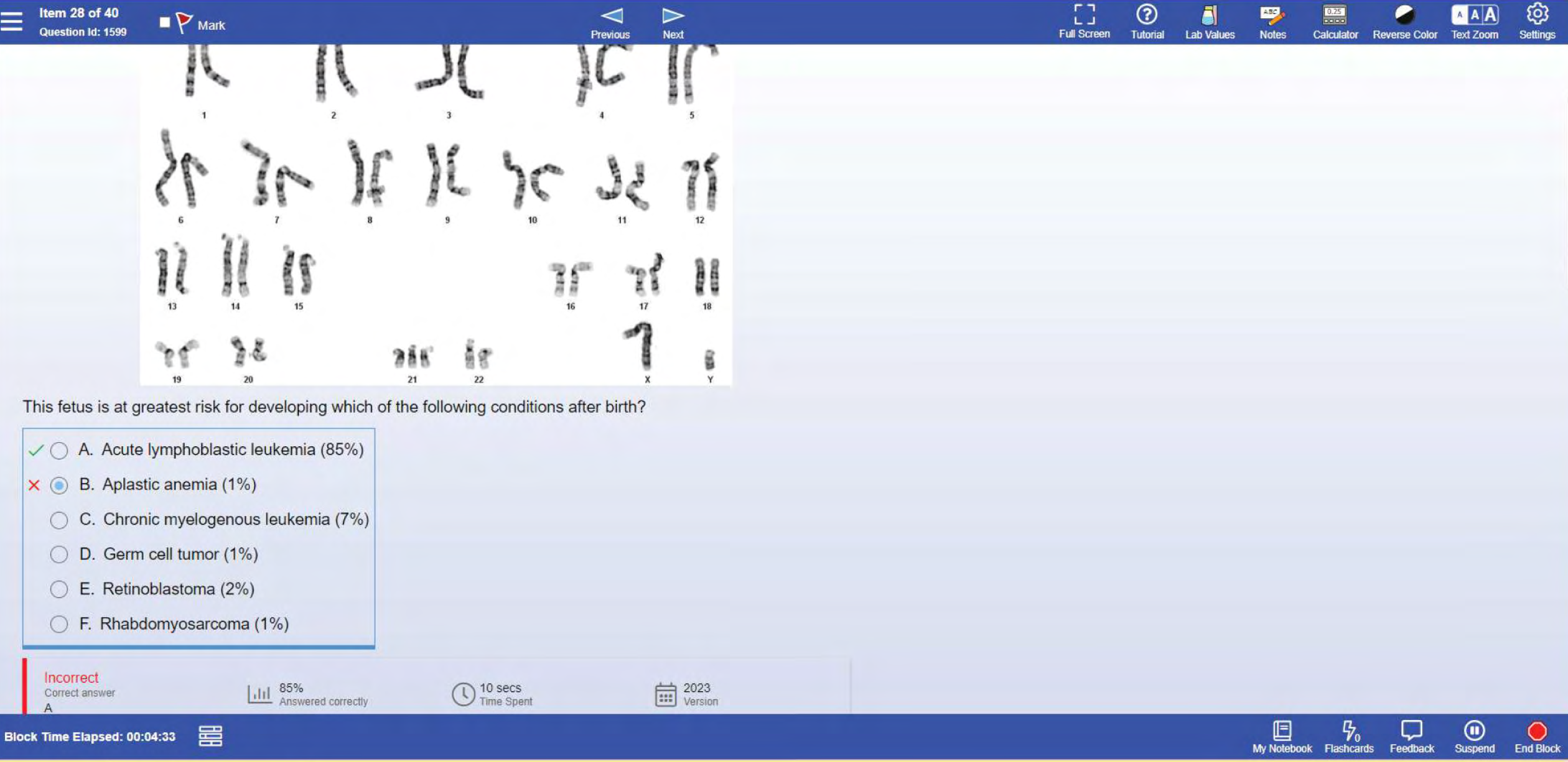
Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
1
2
3
4
5
6
7
8
9
10
11
12
13
14
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16
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Block Time Elapsed: 00:04:33
My Notebook
Flashcards
Feedback
Suspend
End Block

This fetus is at greatest risk for developing which of the following conditions after birth?

✓ ○ A. Acute lymphoblastic leukemia (85%)

✗ ● B. Aplastic anemia (1%)

○ C. Chronic myelogenous leukemia (7%)

○ D. Germ cell tumor (1%)

○ E. Retinoblastoma (2%)

○ F. Rhabdomyosarcoma (1%)

Incorrect
Correct answer
A

85%
Answered correctly

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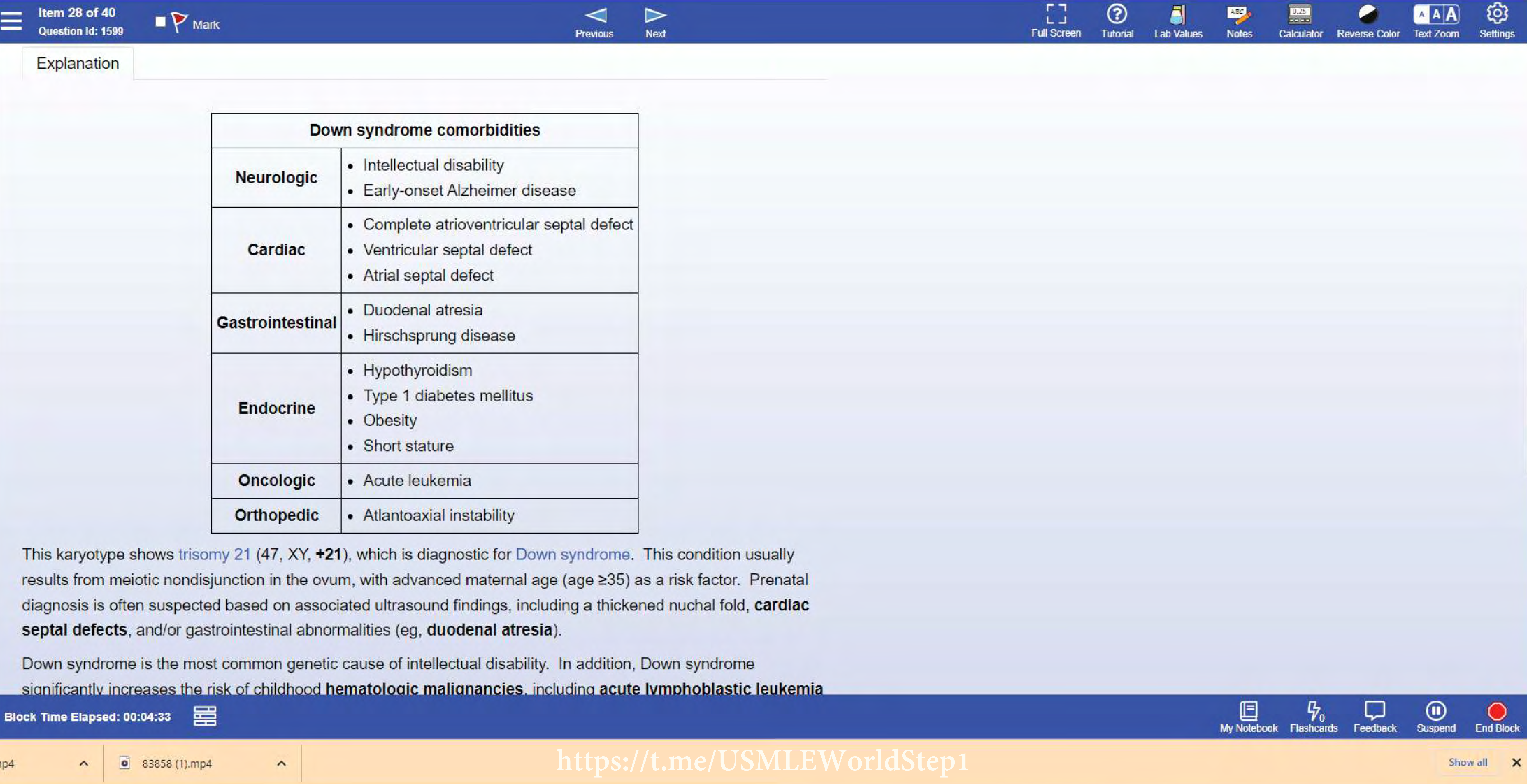
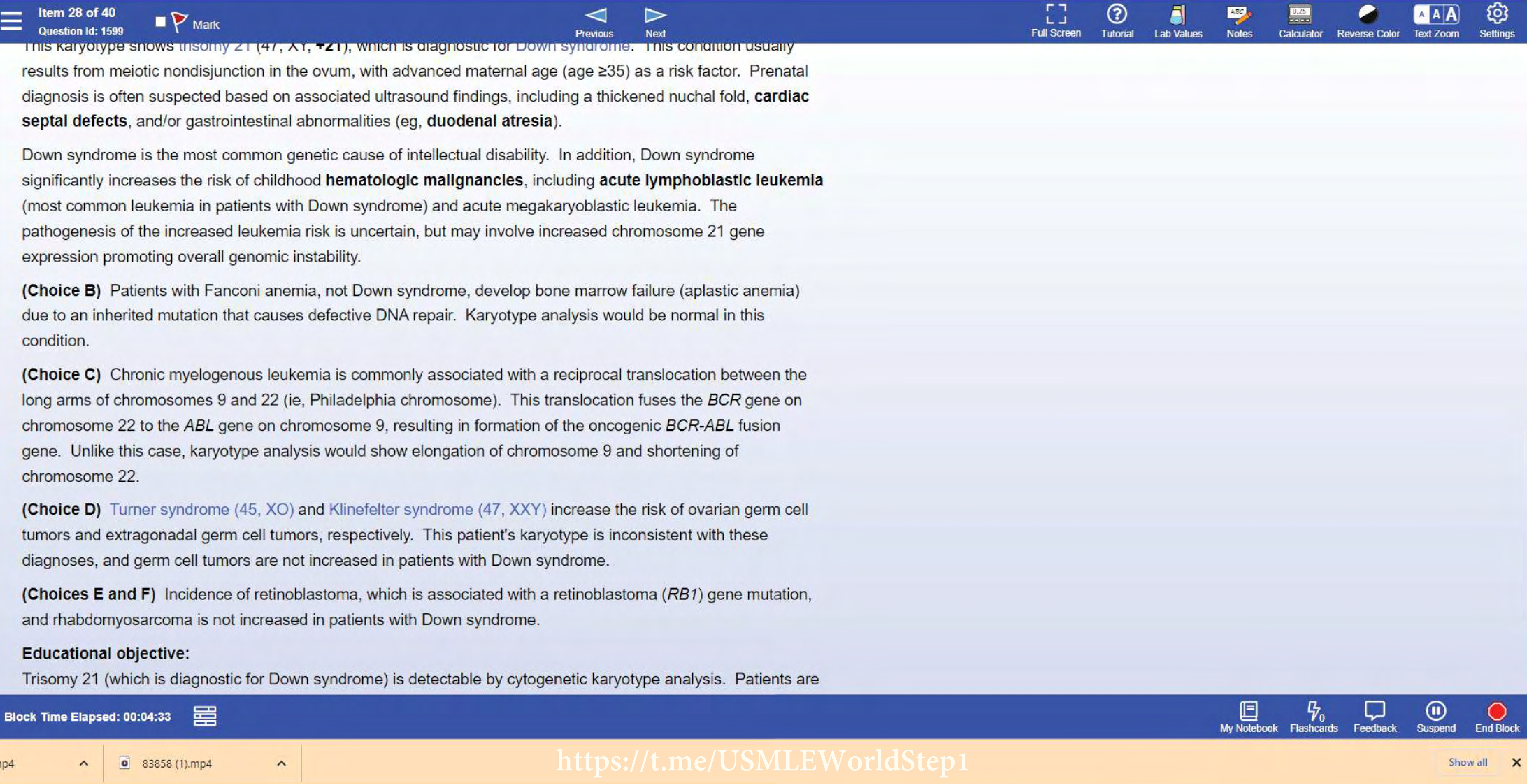

Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Down syndrome comorbidities	
Neurologic	• Intellectual disability • Early-onset Alzheimer disease
Cardiac	• Complete atrioventricular septal defect • Ventricular septal defect • Atrial septal defect
Gastrointestinal	• Duodenal atresia • Hirschsprung disease
Endocrine	• Hypothyroidism • Type 1 diabetes mellitus • Obesity • Short stature
Oncologic	• Acute leukemia
Orthopedic	• Atlantoaxial instability

This karyotype shows trisomy 21 (47, XY, **+21**), which is diagnostic for Down syndrome. This condition usually results from meiotic nondisjunction in the ovum, with advanced maternal age (age ≥35) as a risk factor. Prenatal diagnosis is often suspected based on associated ultrasound findings, including a thickened nuchal fold, **cardiac septal defects**, and/or gastrointestinal abnormalities (eg, **duodenal atresia**).

Down syndrome is the most common genetic cause of intellectual disability. In addition, Down syndrome significantly increases the risk of childhood **hematologic malignancies**, including **acute lymphoblastic leukemia**

Block Time Elapsed: 00:04:33
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all



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Down syndrome is the most common genetic cause of intellectual disability. In addition, Down syndrome significantly increases the risk of childhood **hematologic malignancies**, including **acute lymphoblastic leukemia** (most common leukemia in patients with Down syndrome) and acute megakaryoblastic leukemia. The pathogenesis of the increased leukemia risk is uncertain, but may involve increased chromosome 21 gene expression promoting overall genomic instability.

(Choice B) Patients with Fanconi anemia, not Down syndrome, develop bone marrow failure (aplastic anemia) due to an inherited mutation that causes defective DNA repair. Karyotype analysis would be normal in this condition.

(Choice C) Chronic myelogenous leukemia is commonly associated with a reciprocal translocation between the long arms of chromosomes 9 and 22 (ie, Philadelphia chromosome). This translocation fuses the *BCR* gene on chromosome 22 to the *ABL* gene on chromosome 9, resulting in formation of the oncogenic *BCR-ABL* fusion gene. Unlike this case, karyotype analysis would show elongation of chromosome 9 and shortening of chromosome 22.

(Choice D) Turner syndrome (45, XO) and Klinefelter syndrome (47, XXY) increase the risk of ovarian germ cell tumors and extragonadal germ cell tumors, respectively. This patient's karyotype is inconsistent with these diagnoses, and germ cell tumors are not increased in patients with Down syndrome.

(Choices E and F) Incidence of retinoblastoma, which is associated with a retinoblastoma (*RB1*) gene mutation, and rhabdomyosarcoma is not increased in patients with Down syndrome.

Educational objective:

Trisomy 21 (which is diagnostic for Down syndrome) is detectable by cytogenetic karyotype analysis. Patients are

Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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(Choices E and F) Incidence of retinoblastoma, which is associated with a retinoblastoma (*RB1*) gene mutation, and rhabdomyosarcoma is not increased in patients with Down syndrome.

Educational objective:

Trisomy 21 (which is diagnostic for Down syndrome) is detectable by cytogenetic karyotype analysis. Patients are at increased risk of developing hematologic malignancies, including acute lymphoblastic leukemia and acute megakaryoblastic leukemia.

References

- The biology, pathogenesis and clinical aspects of acute lymphoblastic leukemia in children with Down syndrome.
- Transient abnormal myelopoiesis and AML in Down syndrome: an update.

Genetics	Genetics (General Principles)	Down syndrome
Subject	System	Topic

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My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

Item 28 of 40
Question Id: 1599

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Endocrine

- Type 1 diabetes mellitus

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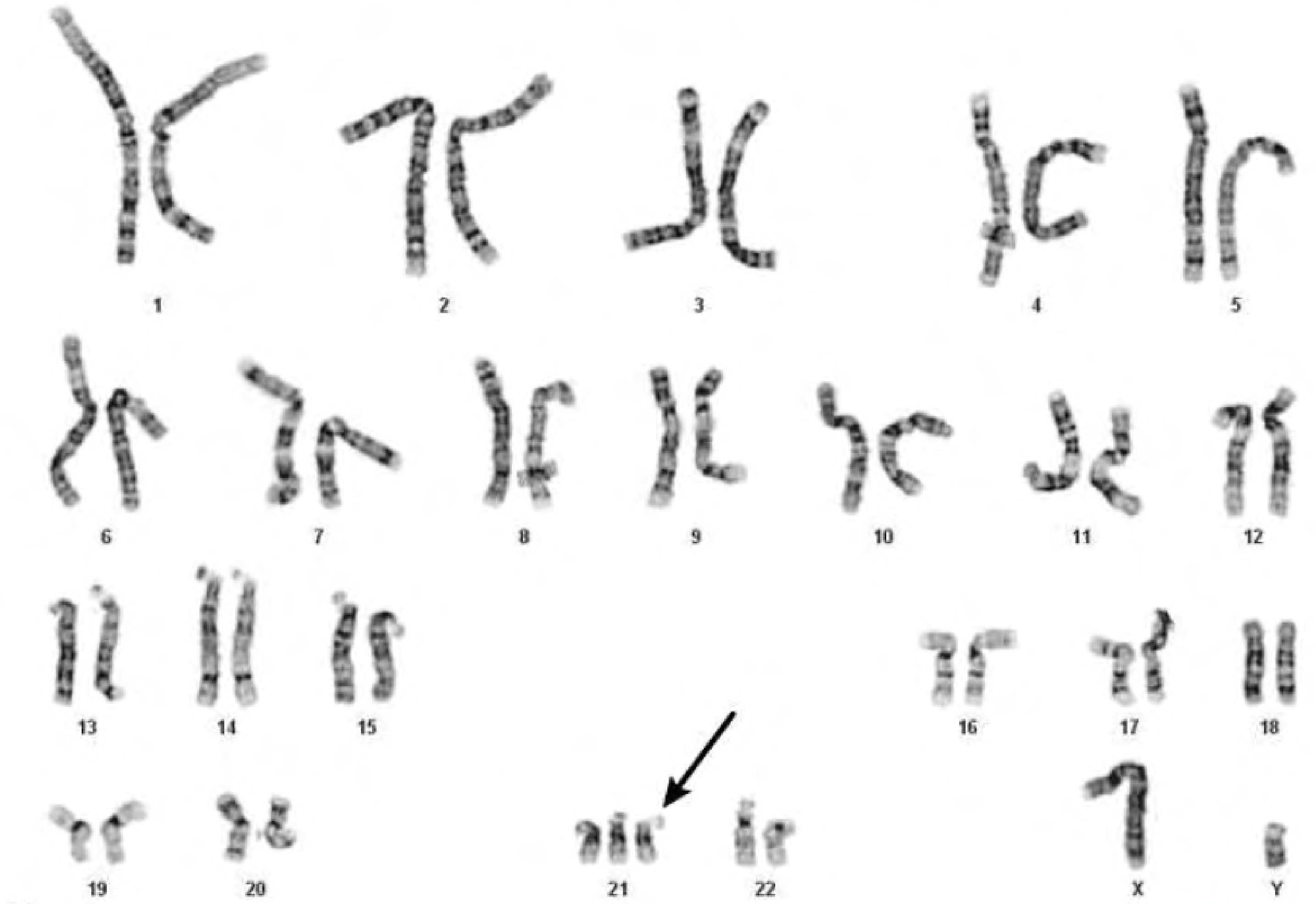
Trisomy 21 (Down syndrome)



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(Choice D) Turner syndrome (45, XO) and Klinefelter syndrome (47, XXY) increase the risk of ovarian germ cell

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My Notebook Flashcards Feedback Suspend End Block

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Item 28 of 40
Question Id: 1599

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Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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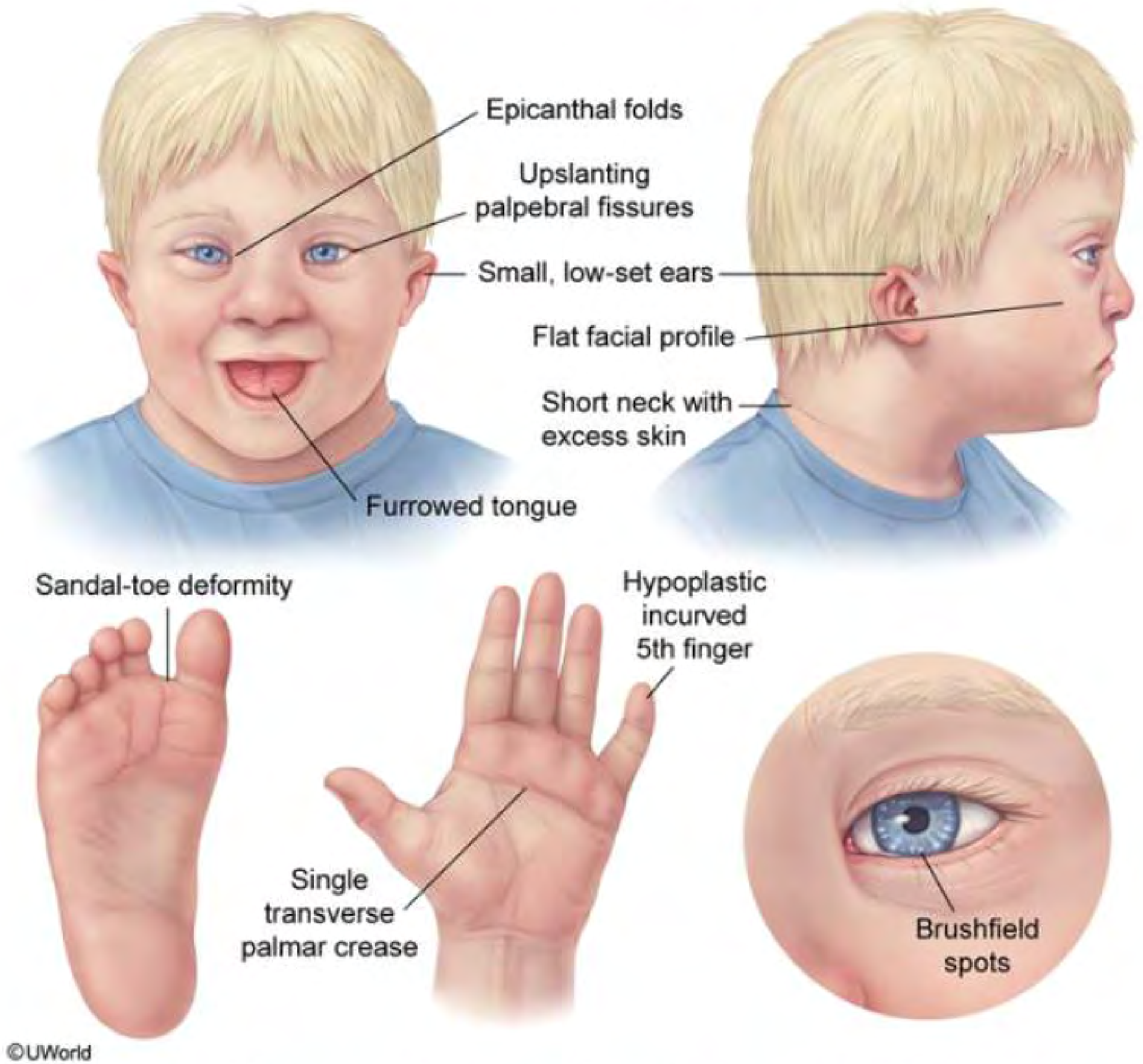
Features of Down syndrome


Epicanthal folds
Upslanting palpebral fissures
Small, low-set ears
Flat facial profile
Short neck with excess skin
Furrowed tongue
Sandal-toe deformity
Hypoplastic incurved 5th finger
Single transverse palmar crease
Brushfield spots

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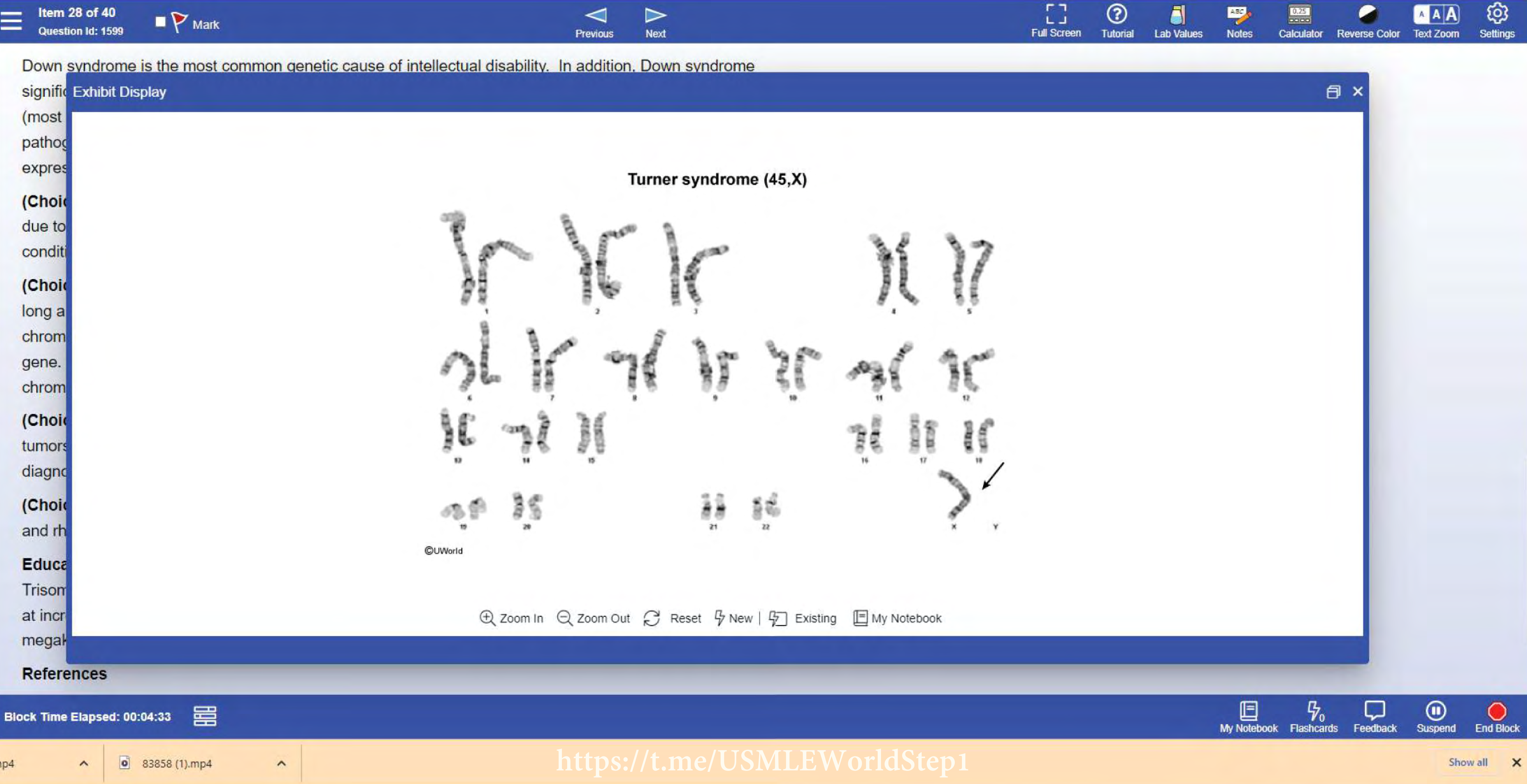
Item 28 of 40
Question Id: 1599
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Zoom In
Zoom Out
Reset
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Block Time Elapsed: 00:04:33
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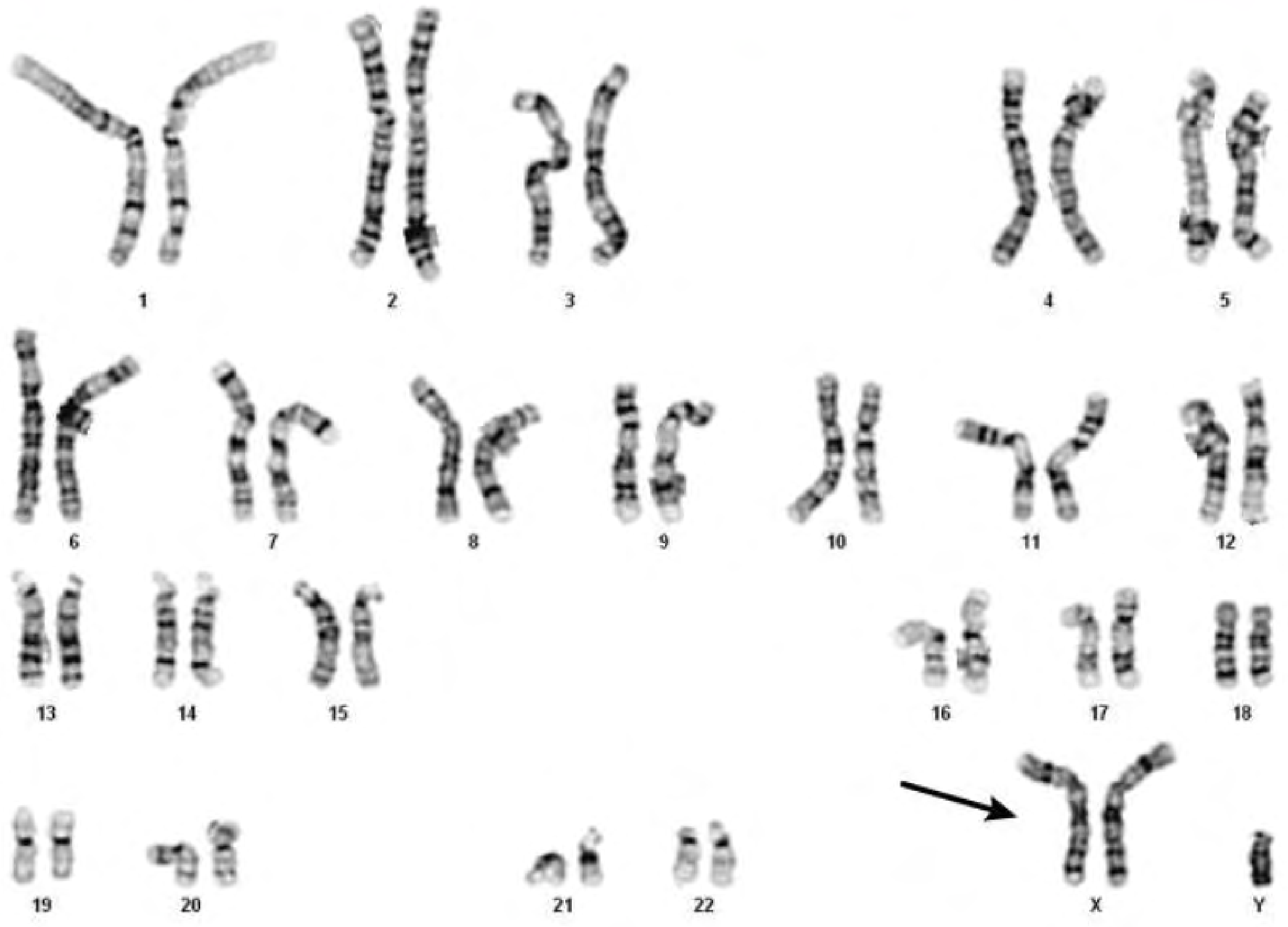
Klinefelter syndrome (47,XXY)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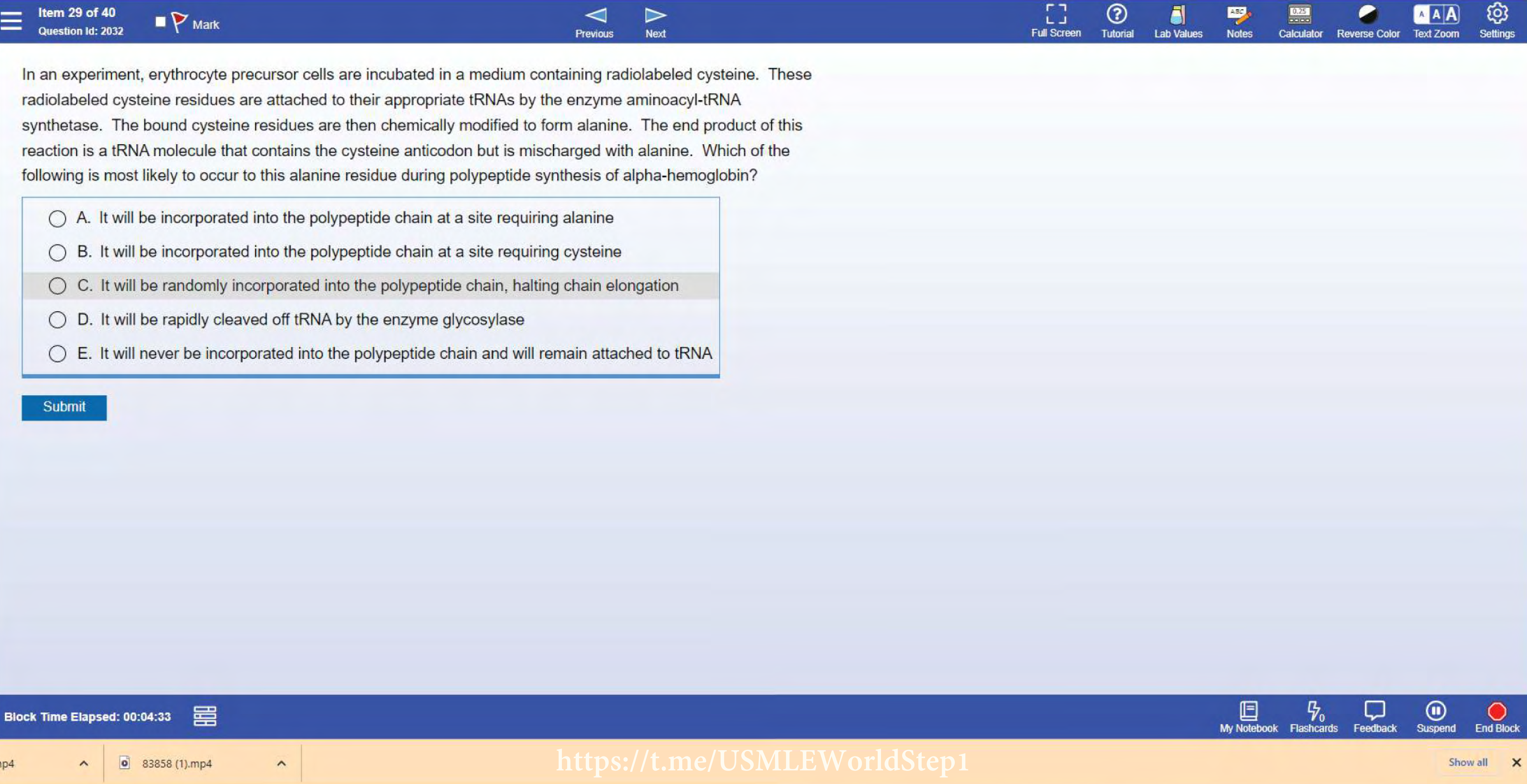
Zoom In
Zoom Out
Reset
New
Existing
My Notebook

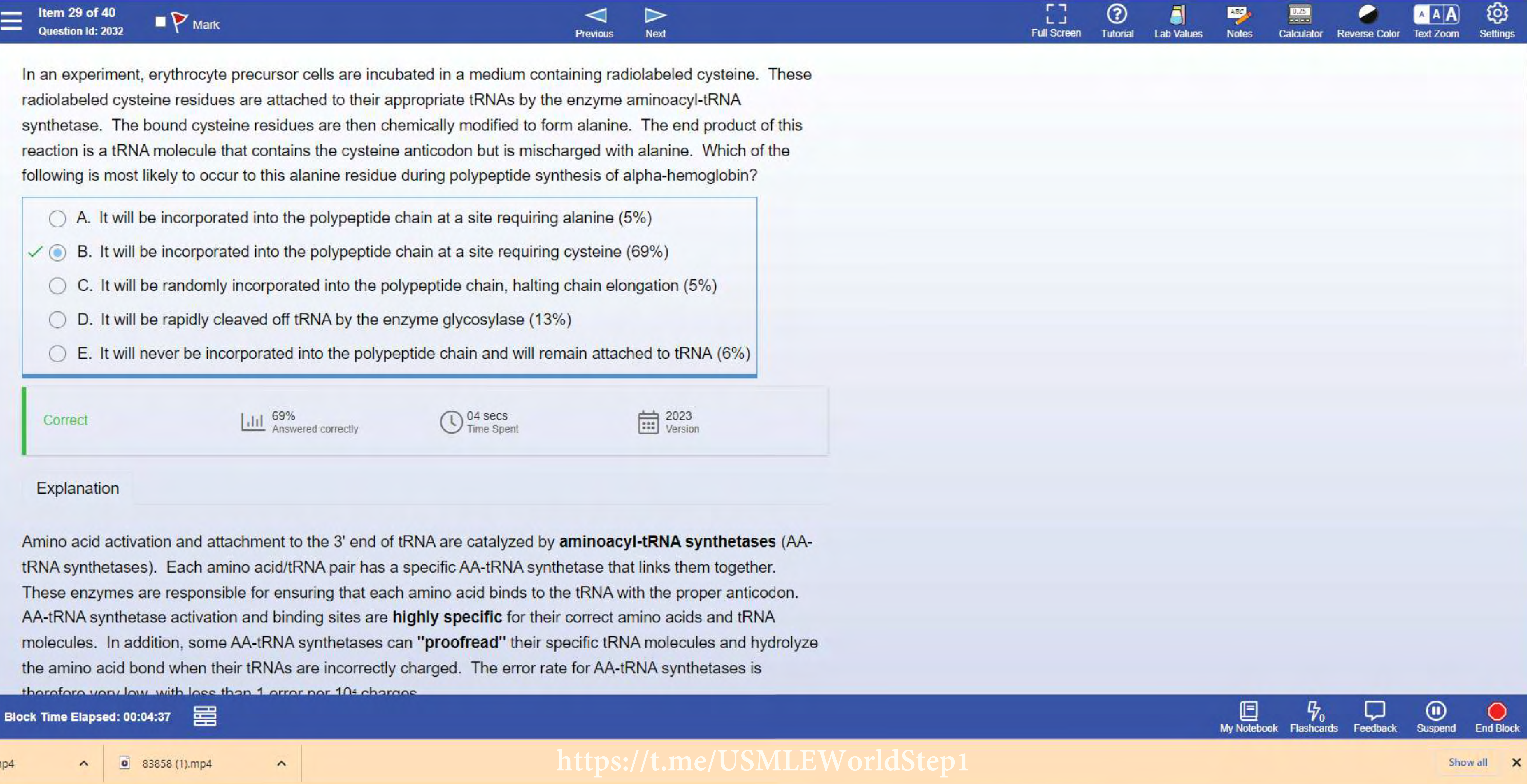
References

p4
83858 (1).mp4
Show all


Item 29 of 40
Question Id: 2032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:04:33
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

○ A. It will be incorporated into the polypeptide chain at a site requiring alanine
○ B. It will be incorporated into the polypeptide chain at a site requiring cysteine
○ C. It will be randomly incorporated into the polypeptide chain, halting chain elongation
○ D. It will be rapidly cleaved off tRNA by the enzyme glycosylase
○ E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA


Item 29 of 40
Question Id: 2032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

- ○ A. It will be incorporated into the polypeptide chain at a site requiring alanine (5%)
- ✓ ● B. It will be incorporated into the polypeptide chain at a site requiring cysteine (69%)
- ○ C. It will be randomly incorporated into the polypeptide chain, halting chain elongation (5%)
- ○ D. It will be rapidly cleaved off tRNA by the enzyme glycosylase (13%)
- ○ E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA (6%)

Correct

69% Answered correctly

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Explanation

Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can **"proofread"** their specific tRNA molecules and hydrolyze the amino acid bond when their tRNAs are incorrectly charged. The error rate for AA-tRNA synthetases is therefore very low, with less than 1 error per 10^4 charges.

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My Notebook
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Feedback
Suspend
End Block
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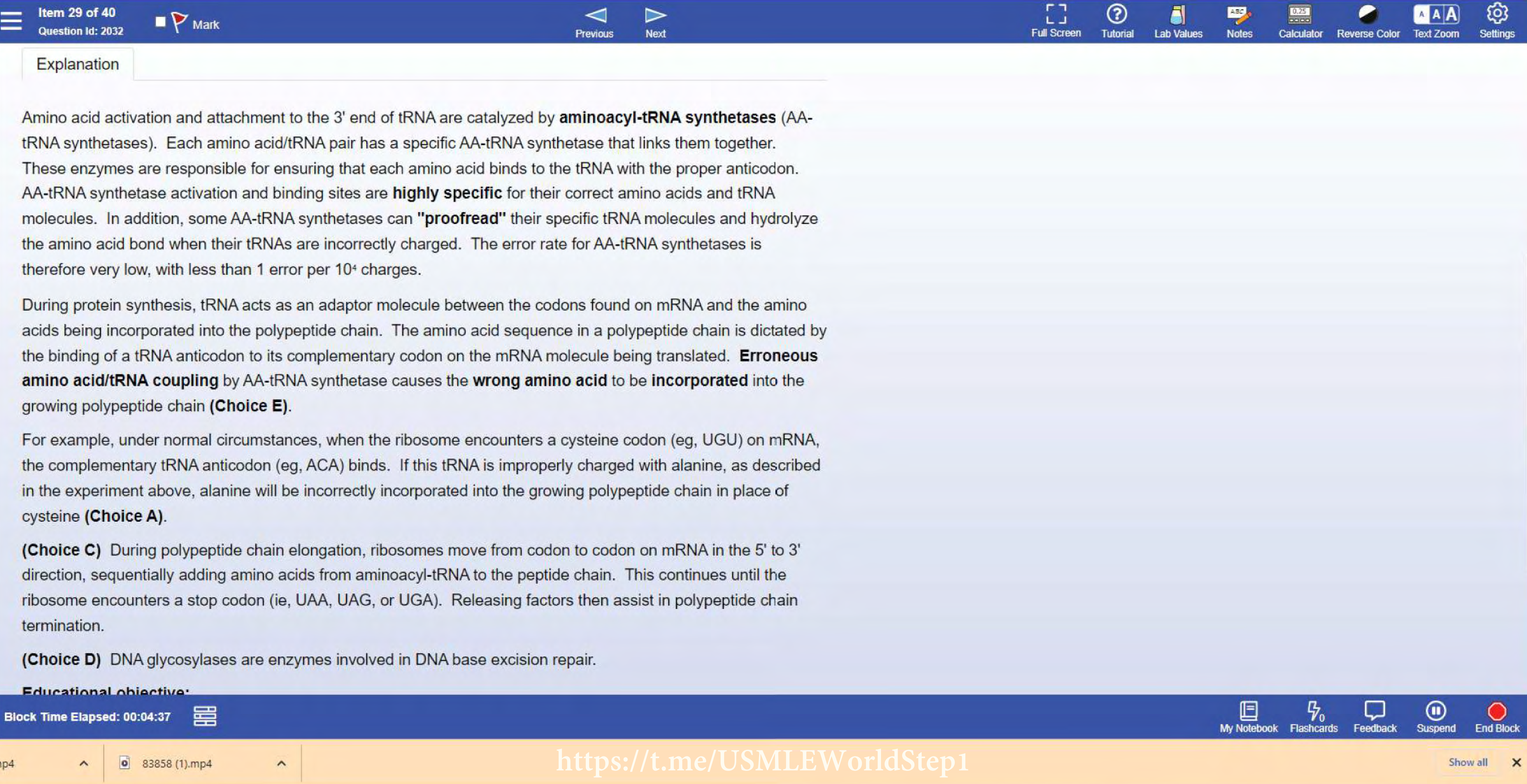
Show all


Item 29 of 40
Question Id: 2032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

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During protein synthesis, tRNA acts as an adaptor molecule between the codons found on mRNA and the amino acids being incorporated into the polypeptide chain. The amino acid sequence in a polypeptide chain is dictated by the binding of a tRNA anticodon to its complementary codon on the mRNA molecule being translated. **Erroneous amino acid/tRNA coupling** by AA-tRNA synthetase causes the **wrong amino acid** to be **incorporated** into the growing polypeptide chain **(Choice E)**.

For example, under normal circumstances, when the ribosome encounters a cysteine codon (eg, UGU) on mRNA, the complementary tRNA anticodon (eg, ACA) binds. If this tRNA is improperly charged with alanine, as described in the experiment above, alanine will be incorrectly incorporated into the growing polypeptide chain in place of cysteine **(Choice A)**.

(Choice C) During polypeptide chain elongation, ribosomes move from codon to codon on mRNA in the 5' to 3' direction, sequentially adding amino acids from aminoacyl-tRNA to the peptide chain. This continues until the ribosome encounters a stop codon (ie, UAA, UAG, or UGA). Releasing factors then assist in polypeptide chain termination.

(Choice D) DNA glycosylases are enzymes involved in DNA base excision repair.

Educational objective:

Block Time Elapsed: 00:04:37
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

Item 29 of 40
Question Id: 2032
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

During protein synthesis, tRNA acts as an adaptor molecule between the codons found on mRNA and the amino acids being incorporated into the polypeptide chain. The amino acid sequence in a polypeptide chain is dictated by the binding of a tRNA anticodon to its complementary codon on the mRNA molecule being translated. **Erroneous amino acid/tRNA coupling** by AA-tRNA synthetase causes the **wrong amino acid** to be **incorporated** into the growing polypeptide chain **(Choice E)**.

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(Choice D) DNA glycosylases are enzymes involved in DNA base excision repair.

Educational objective:

The sequence of amino acids in a growing polypeptide chain is dictated by the interaction of the mRNA codon with the tRNA anticodon. tRNA that is mischarged with the incorrect amino acid (and not corrected by aminoacyl-tRNA synthetase proofreading) will incorporate the wrong amino acid into the growing polypeptide chain.

References

- Quality control in aminoacyl-tRNA synthesis its role in translational fidelity.

Genetics	Genetics (General Principles)	Rna structure & function
Subject	System	Topic

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Block Time Elapsed: 00:04:37
My Notebook
Flashcards
Feedback
Suspend
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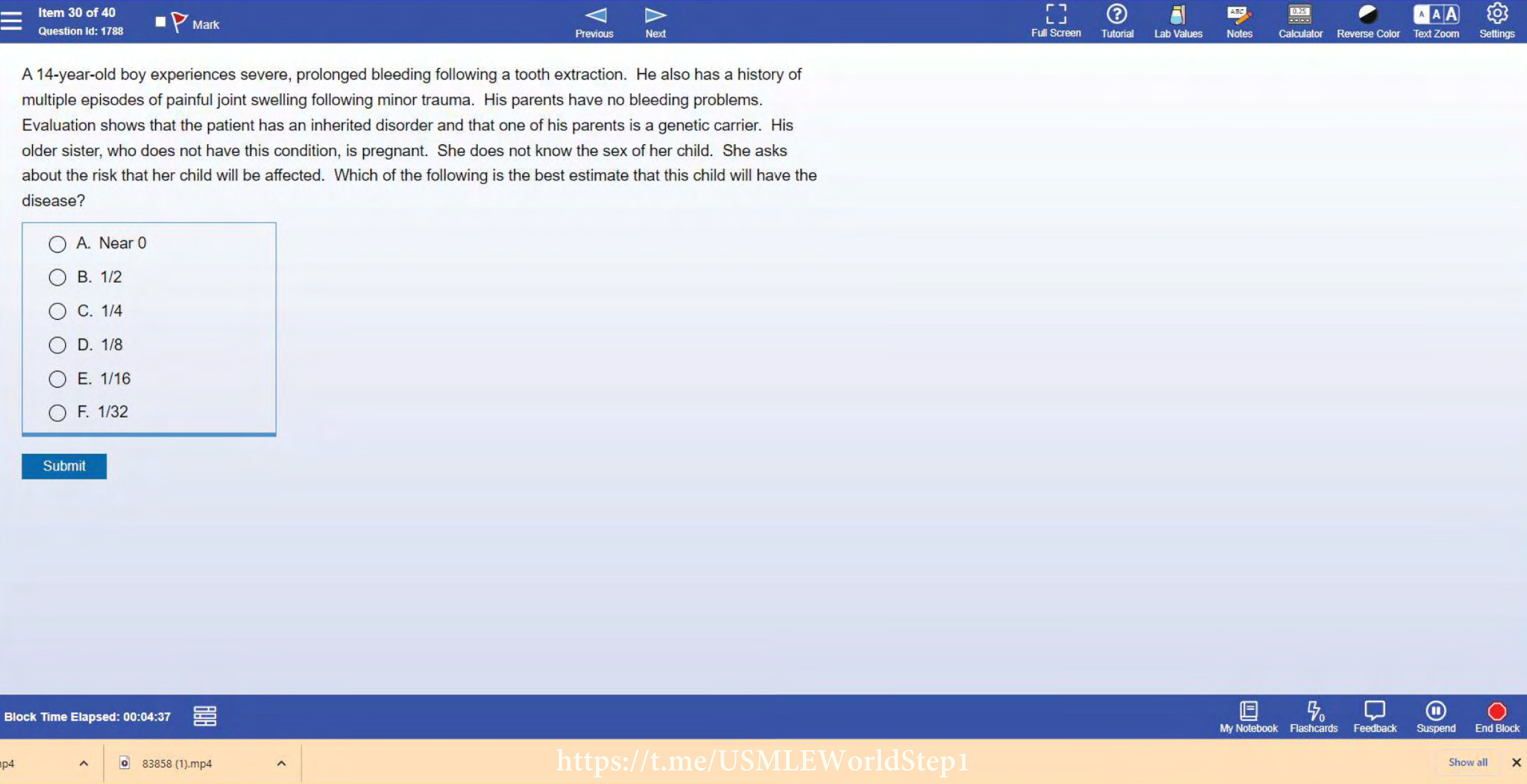
p4
83858 (1).mp4
Show all


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

Item 30 of 40
Question Id: 1788

A 14-year-old boy experiences severe, prolonged bleeding following a tooth extraction. He also has a history of multiple episodes of painful joint swelling following minor trauma. His parents have no bleeding problems. Evaluation shows that the patient has an inherited disorder and that one of his parents is a genetic carrier. His older sister, who does not have this condition, is pregnant. She does not know the sex of her child. She asks about the risk that her child will be affected. Which of the following is the best estimate that this child will have the disease?

○ A. Near 0
○ B. 1/2
○ C. 1/4
○ D. 1/8
○ E. 1/16
○ F. 1/32

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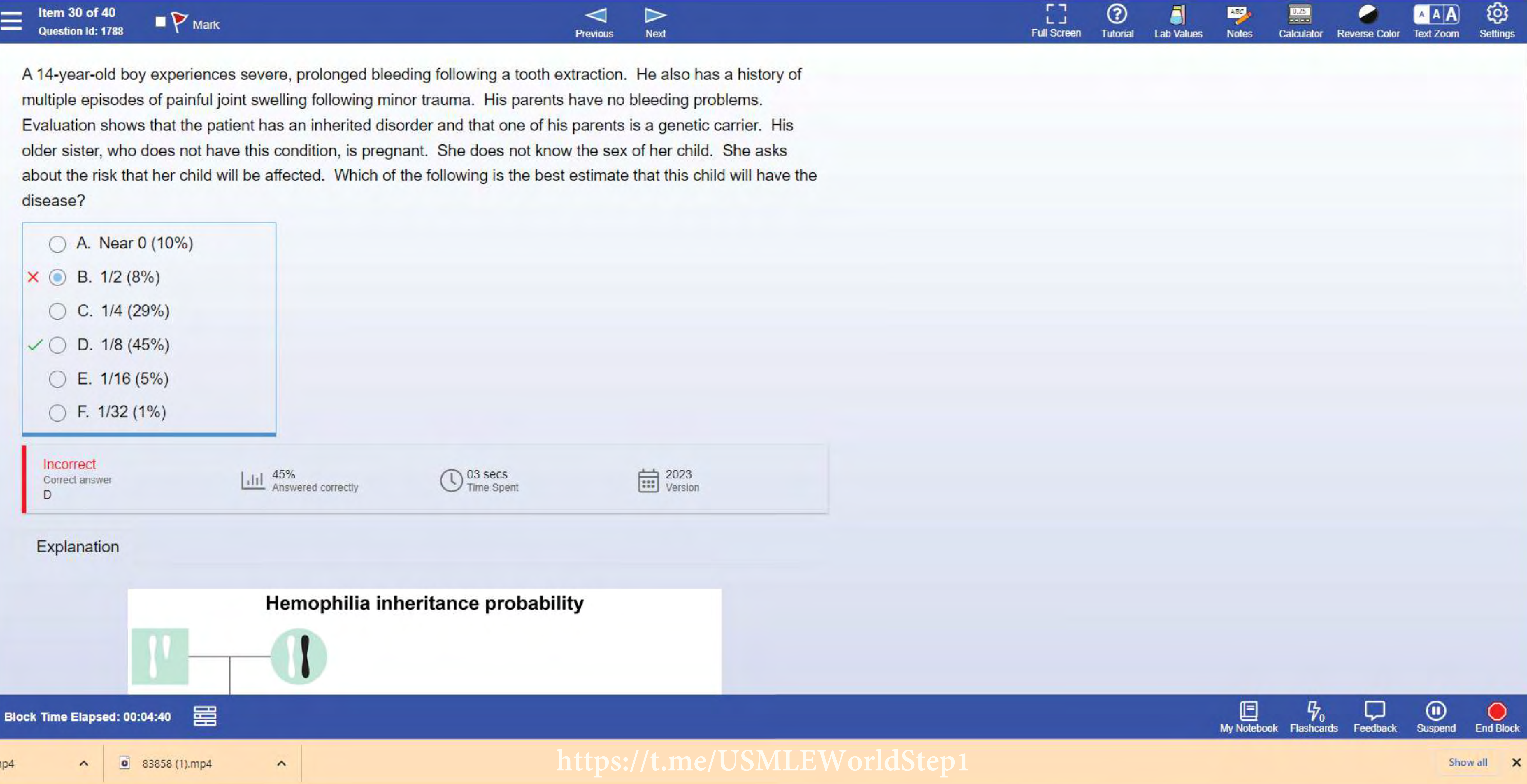
Item 30 of 40
Question Id: 1788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Near 0 (10%)

✗ ● B. 1/2 (8%)

○ C. 1/4 (29%)

✓ ○ D. 1/8 (45%)

○ E. 1/16 (5%)

○ F. 1/32 (1%)

Incorrect
Correct answer
D

45%
Answered correctly

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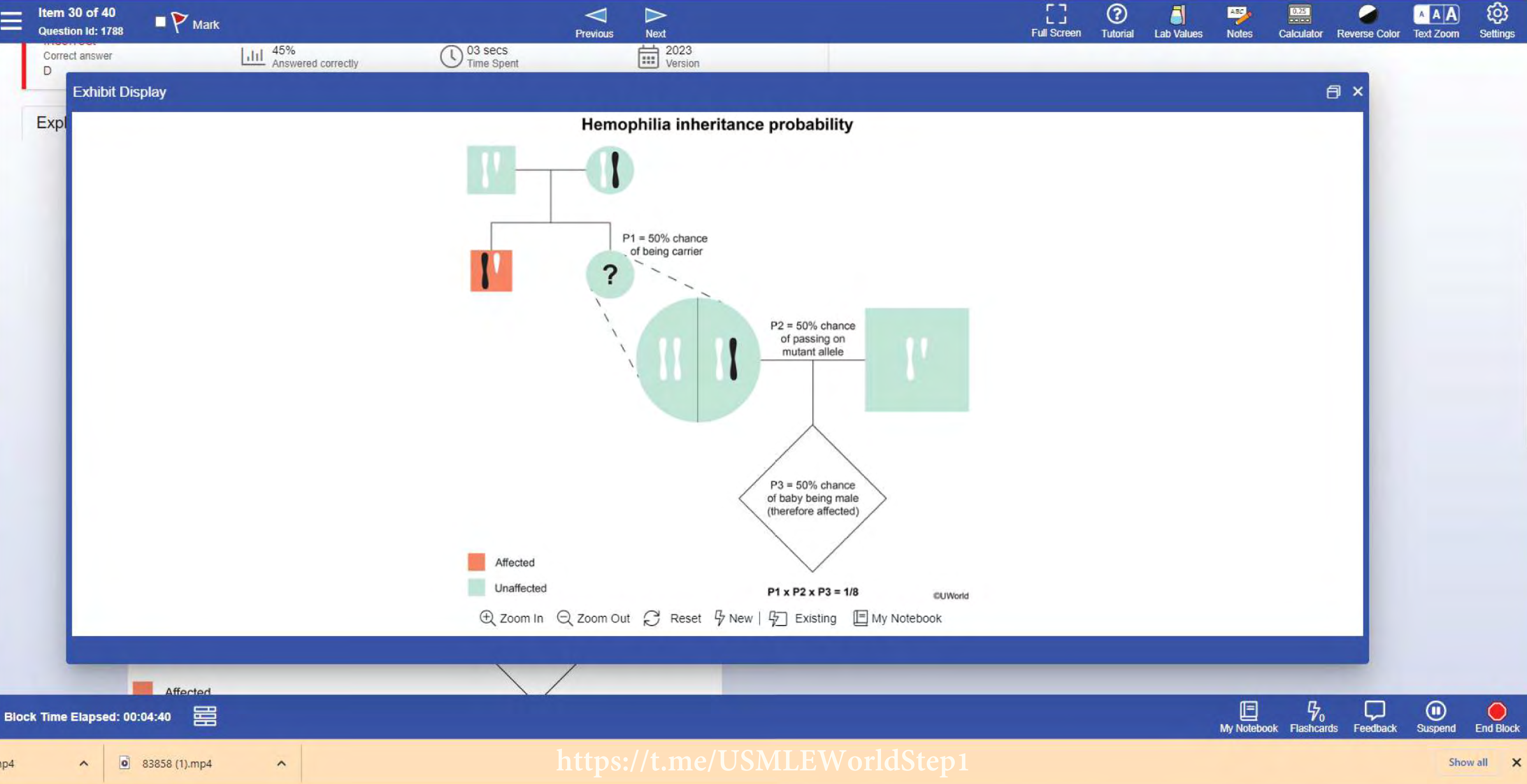
Time Spent

2023
Version

Explanation

Hemophilia inheritance probability

Block Time Elapsed: 00:04:40
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 30 of 40
Question Id: 1788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Correct answer
D

45%
Answered correctly

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Time Spent

2023
Version

Exhibit Display
Expl

Hemophilia inheritance probability

P1 = 50% chance of being carrier

P2 = 50% chance of passing on mutant allele

P3 = 50% chance of baby being male (therefore affected)

🟥 Affected

🟩 Unaffected

P1 x P2 x P3 = 1/8

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Zoom Out
Reset
New
Existing
My Notebook
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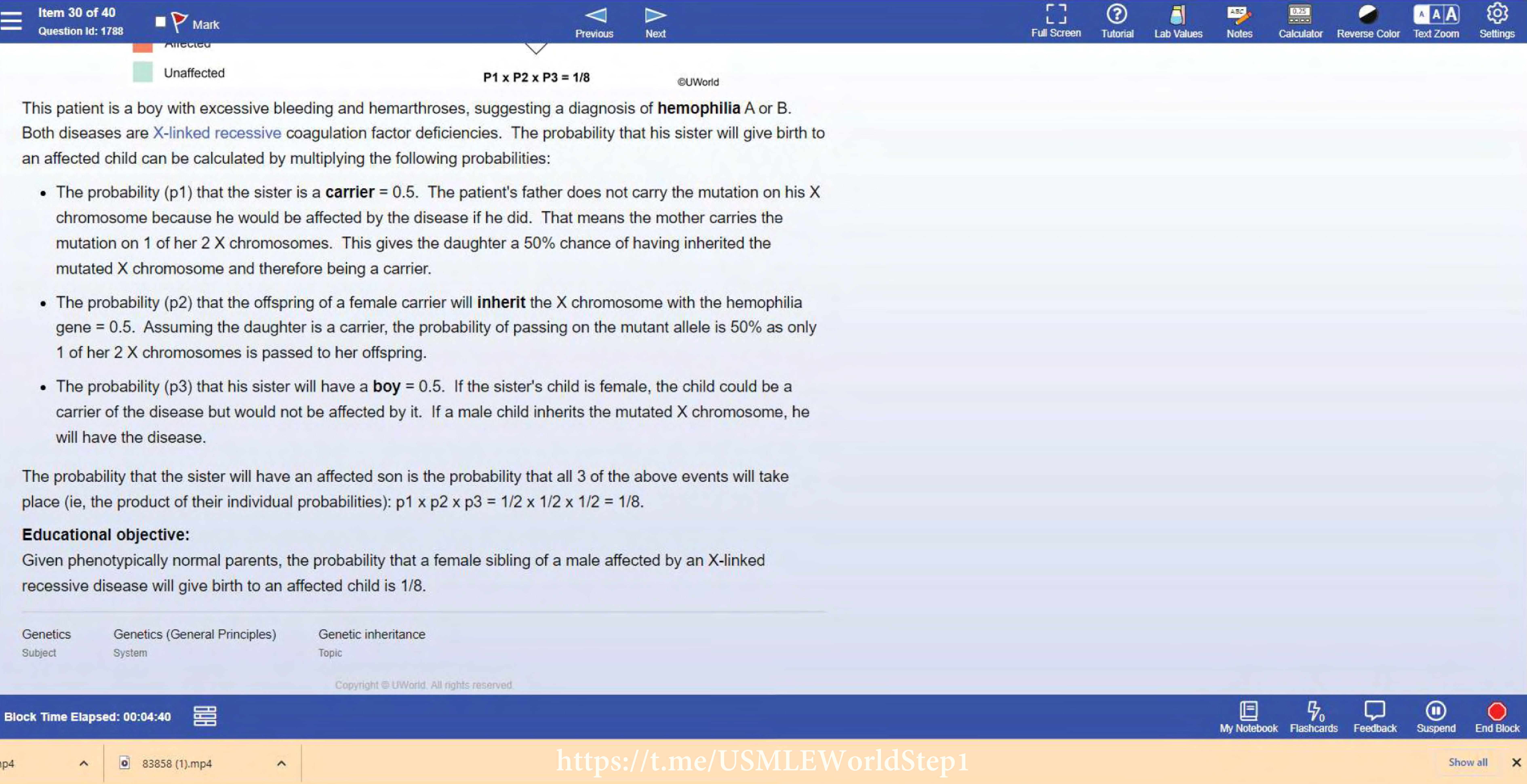
Block Time Elapsed: 00:04:40

My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 30 of 40
Question Id: 1788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Affected
Unaffected
P1 x P2 x P3 = 1/8
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🟥 Affected

🟩 Unaffected

This patient is a boy with excessive bleeding and hemarthroses, suggesting a diagnosis of **hemophilia** A or B. Both diseases are X-linked recessive coagulation factor deficiencies. The probability that his sister will give birth to an affected child can be calculated by multiplying the following probabilities:

- The probability (p1) that the sister is a **carrier** = 0.5. The patient's father does not carry the mutation on his X chromosome because he would be affected by the disease if he did. That means the mother carries the mutation on 1 of her 2 X chromosomes. This gives the daughter a 50% chance of having inherited the mutated X chromosome and therefore being a carrier.
- The probability (p2) that the offspring of a female carrier will **inherit** the X chromosome with the hemophilia gene = 0.5. Assuming the daughter is a carrier, the probability of passing on the mutant allele is 50% as only 1 of her 2 X chromosomes is passed to her offspring.
- The probability (p3) that his sister will have a **boy** = 0.5. If the sister's child is female, the child could be a carrier of the disease but would not be affected by it. If a male child inherits the mutated X chromosome, he will have the disease.

The probability that the sister will have an affected son is the probability that all 3 of the above events will take place (ie, the product of their individual probabilities): p1 x p2 x p3 = 1/2 x 1/2 x 1/2 = 1/8.

Educational objective:
Given phenotypically normal parents, the probability that a female sibling of a male affected by an X-linked recessive disease will give birth to an affected child is 1/8.

Genetics	Genetics (General Principles)	Genetic inheritance
Subject	System	Topic

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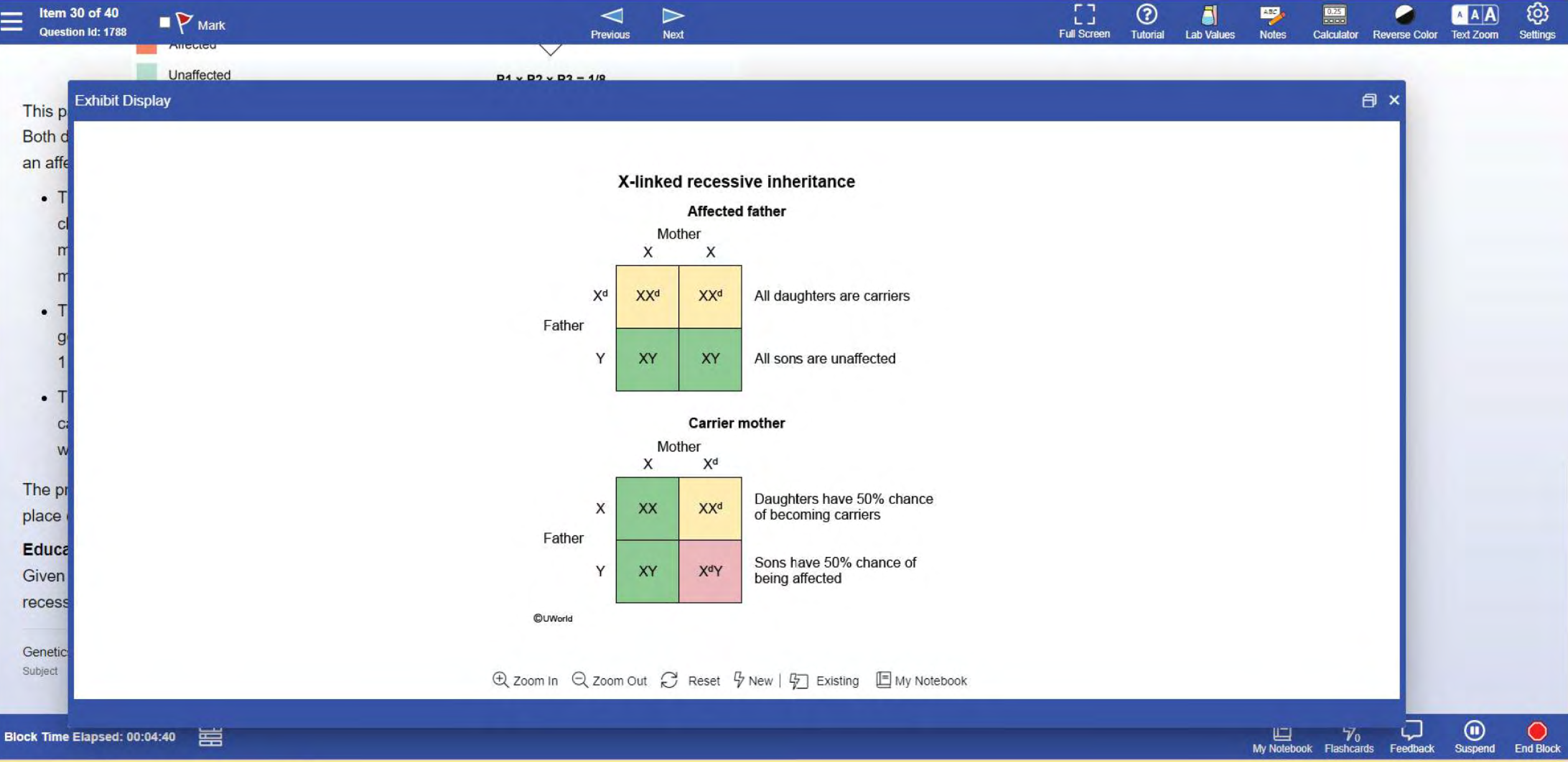
Block Time Elapsed: 00:04:40
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 30 of 40
Question Id: 1788
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Unaffected
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:04:40
My Notebook
Flashcards
Feedback
Suspend
End Block

X-linked recessive inheritance

Affected father

Mother

Father

	X	X	
X^d	XX^d	XX^d	All daughters are carriers
Y	XY	XY	All sons are unaffected

Carrier mother

Mother

Father

	X	X^d	
X	XX	XX^d	Daughters have 50% chance of becoming carriers
Y	XY	X^dY	Sons have 50% chance of being affected

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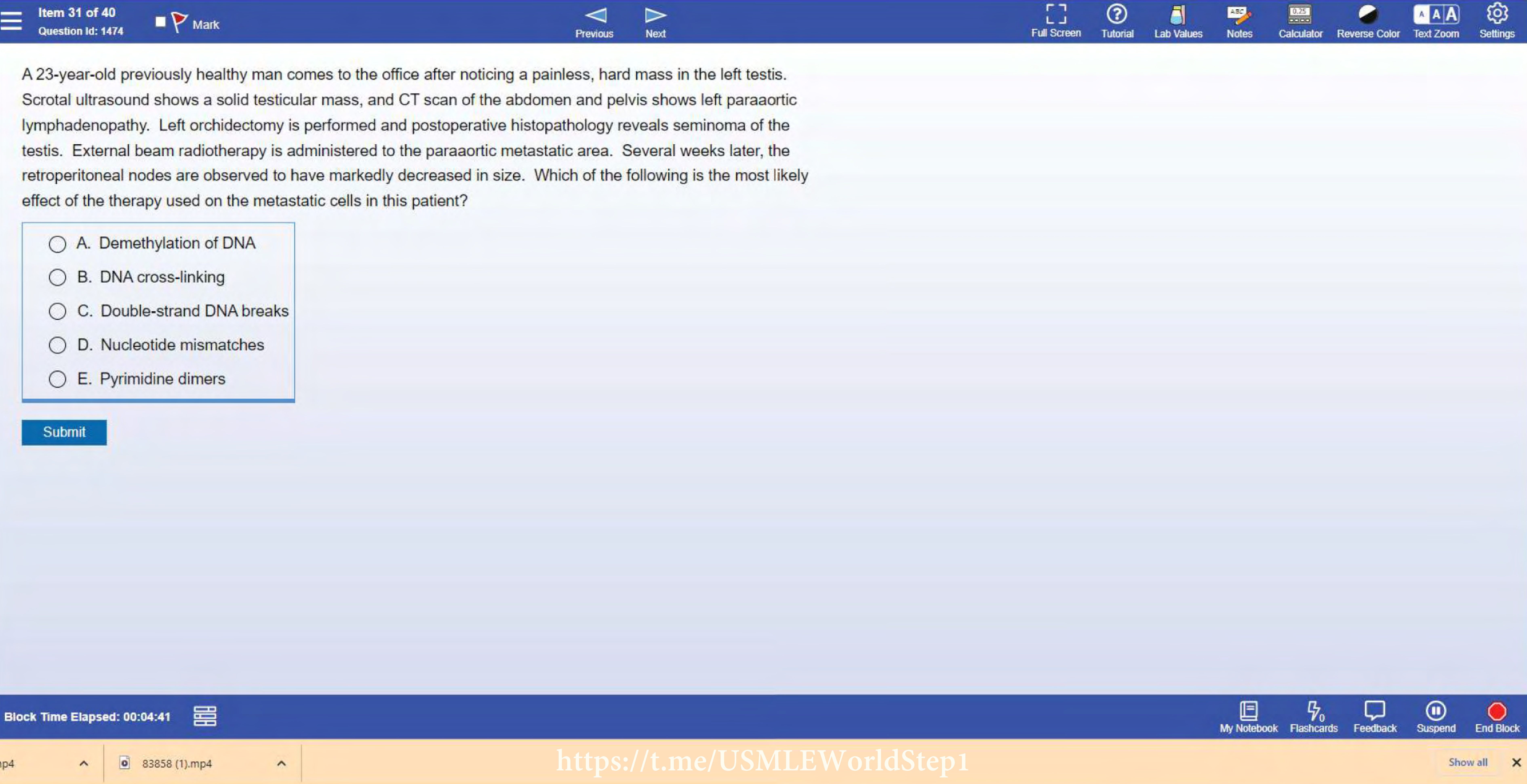

Item 31 of 40
Question Id: 1474
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 23-year-old previously healthy man comes to the office after noticing a painless, hard mass in the left testis. Scrotal ultrasound shows a solid testicular mass, and CT scan of the abdomen and pelvis shows left paraaortic lymphadenopathy. Left orchidectomy is performed and postoperative histopathology reveals seminoma of the testis. External beam radiotherapy is administered to the paraaortic metastatic area. Several weeks later, the retroperitoneal nodes are observed to have markedly decreased in size. Which of the following is the most likely effect of the therapy used on the metastatic cells in this patient?

○ A. Demethylation of DNA
○ B. DNA cross-linking
○ C. Double-strand DNA breaks
○ D. Nucleotide mismatches
○ E. Pyrimidine dimers

Submit
Block Time Elapsed: 00:04:41
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
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- ○ A. Demethylation of DNA (4%)
- ✗ ● B. DNA cross-linking (10%)
- ✓ ○ C. Double-strand DNA breaks (64%)
- ○ D. Nucleotide mismatches (2%)
- ○ E. Pyrimidine dimers (17%)

Incorrect
Correct answer
C

64%
Answered correctly

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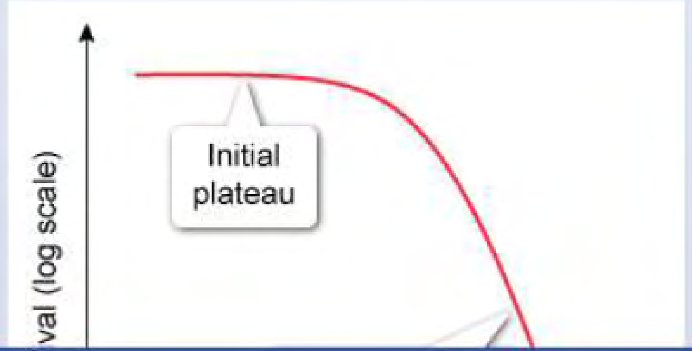
2023
Version

Explanation



p4
83858 (1).mp4
Show all

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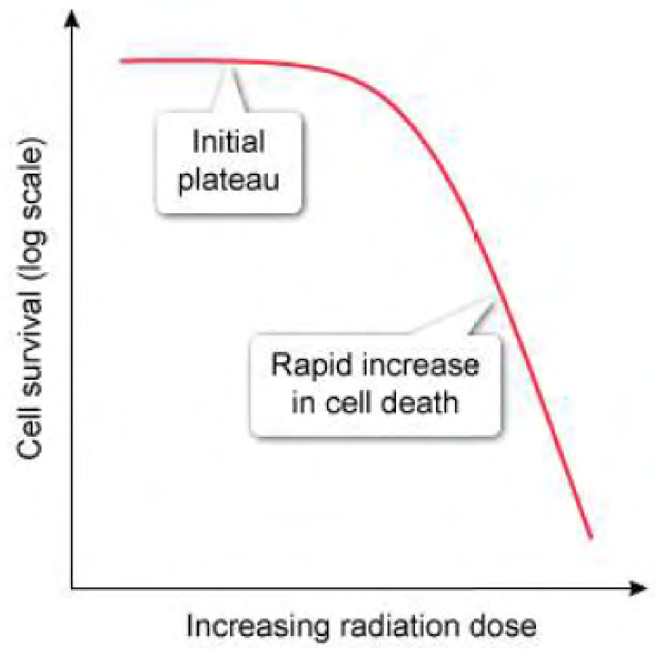

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A characteristic cell death curve of exposure to radiation shows a nearly flat line on initial exposure, followed by a

p4 83858 (1).mp4
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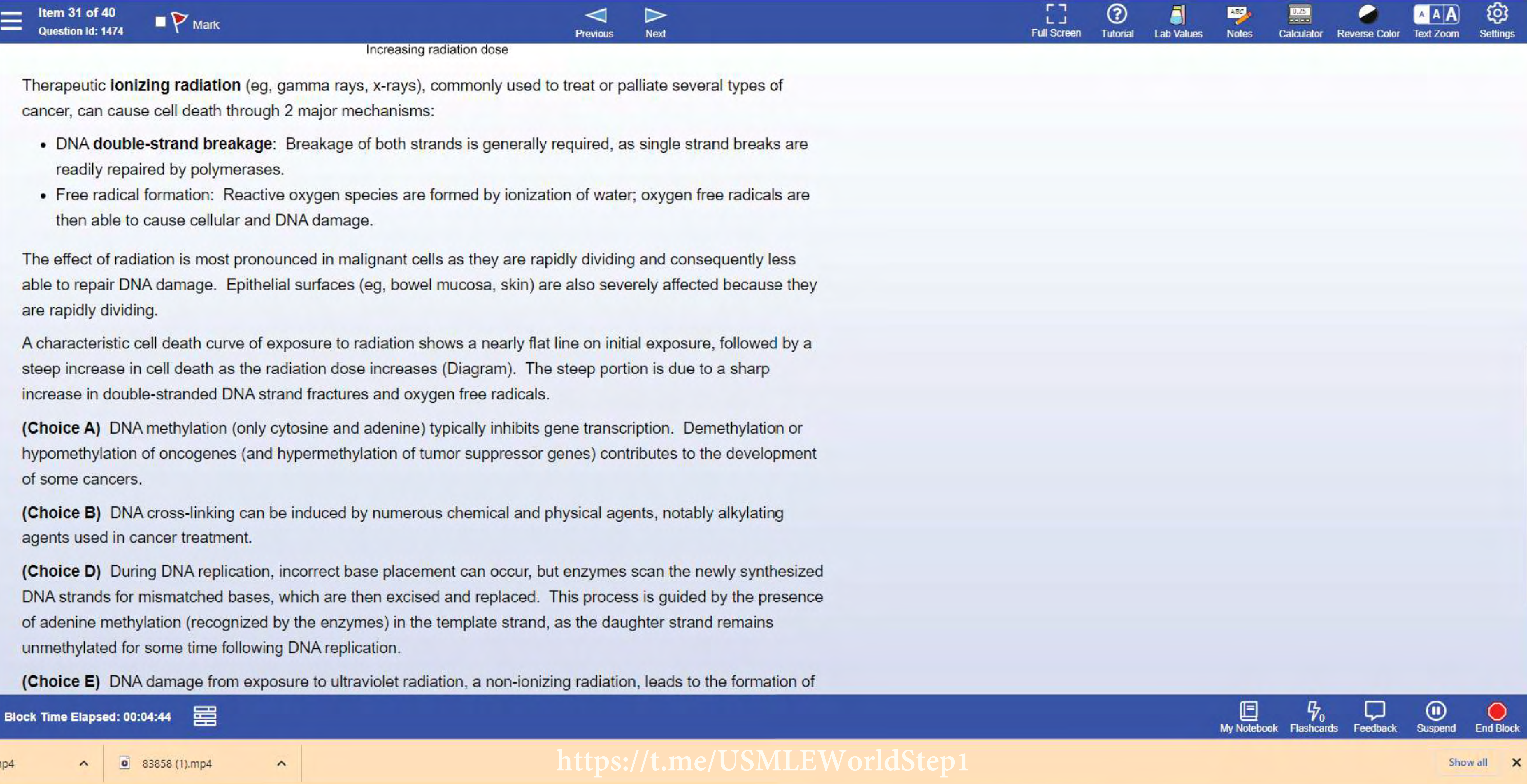

Item 31 of 40
Question Id: 1474
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Increasing radiation dose
Block Time Elapsed: 00:04:44
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all

Therapeutic **ionizing radiation** (eg, gamma rays, x-rays), commonly used to treat or palliate several types of cancer, can cause cell death through 2 major mechanisms:

- DNA **double-strand breakage**: Breakage of both strands is generally required, as single strand breaks are readily repaired by polymerases.
- Free radical formation: Reactive oxygen species are formed by ionization of water; oxygen free radicals are then able to cause cellular and DNA damage.

The effect of radiation is most pronounced in malignant cells as they are rapidly dividing and consequently less able to repair DNA damage. Epithelial surfaces (eg, bowel mucosa, skin) are also severely affected because they are rapidly dividing.

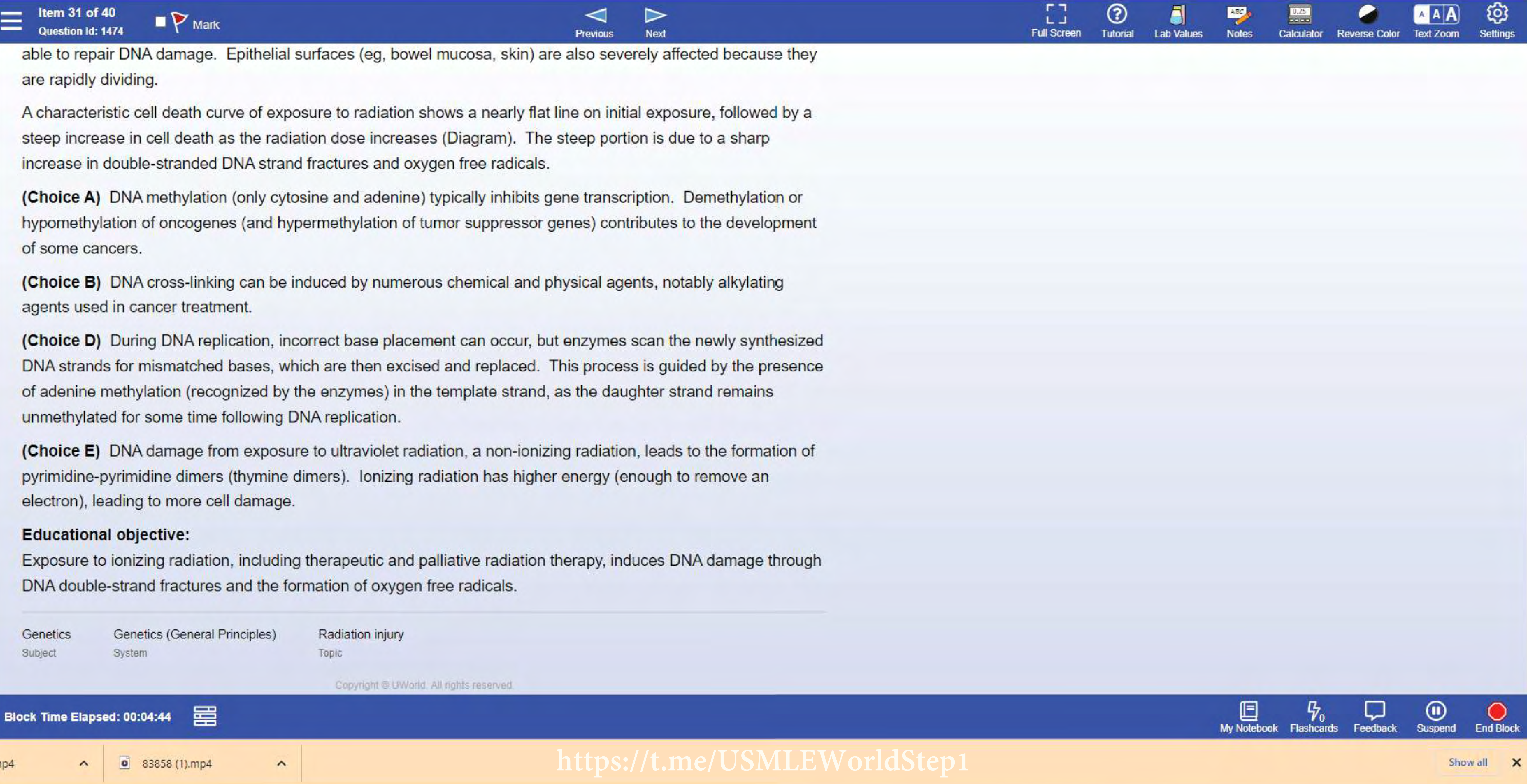
A characteristic cell death curve of exposure to radiation shows a nearly flat line on initial exposure, followed by a steep increase in cell death as the radiation dose increases (Diagram). The steep portion is due to a sharp increase in double-stranded DNA strand fractures and oxygen free radicals.

(Choice A) DNA methylation (only cytosine and adenine) typically inhibits gene transcription. Demethylation or hypomethylation of oncogenes (and hypermethylation of tumor suppressor genes) contributes to the development of some cancers.

(Choice B) DNA cross-linking can be induced by numerous chemical and physical agents, notably alkylating agents used in cancer treatment.

(Choice D) During DNA replication, incorrect base placement can occur, but enzymes scan the newly synthesized DNA strands for mismatched bases, which are then excised and replaced. This process is guided by the presence of adenine methylation (recognized by the enzymes) in the template strand, as the daughter strand remains unmethylated for some time following DNA replication.

(Choice E) DNA damage from exposure to ultraviolet radiation, a non-ionizing radiation, leads to the formation of


Item 31 of 40
Question Id: 1474
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

able to repair DNA damage. Epithelial surfaces (eg, bowel mucosa, skin) are also severely affected because they are rapidly dividing.

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(Choice E) DNA damage from exposure to ultraviolet radiation, a non-ionizing radiation, leads to the formation of pyrimidine-pyrimidine dimers (thymine dimers). Ionizing radiation has higher energy (enough to remove an electron), leading to more cell damage.

Educational objective:

Exposure to ionizing radiation, including therapeutic and palliative radiation therapy, induces DNA damage through DNA double-strand fractures and the formation of oxygen free radicals.

Genetics	Genetics (General Principles)	Radiation injury
Subject	System	Topic

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Block Time Elapsed: 00:04:44
My Notebook
Flashcards
Feedback
Suspend
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p4
83858 (1).mp4
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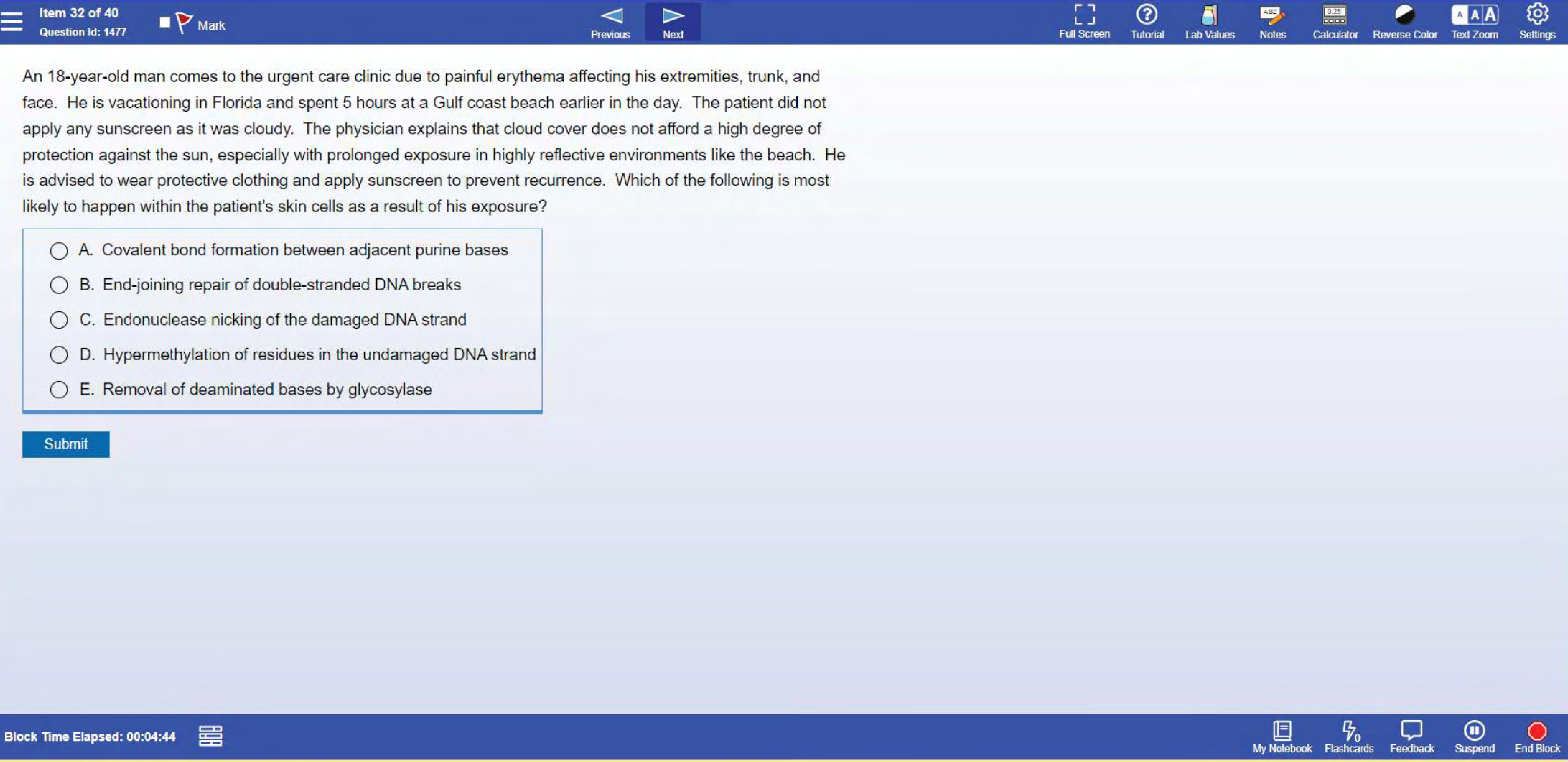
Item 32 of 40
Question Id: 1477
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 18-year-old man comes to the urgent care clinic due to painful erythema affecting his extremities, trunk, and face. He is vacationing in Florida and spent 5 hours at a Gulf coast beach earlier in the day. The patient did not apply any sunscreen as it was cloudy. The physician explains that cloud cover does not afford a high degree of protection against the sun, especially with prolonged exposure in highly reflective environments like the beach. He is advised to wear protective clothing and apply sunscreen to prevent recurrence. Which of the following is most likely to happen within the patient's skin cells as a result of his exposure?

- ○ A. Covalent bond formation between adjacent purine bases
- ○ B. End-joining repair of double-stranded DNA breaks
- ○ C. Endonuclease nicking of the damaged DNA strand
- ○ D. Hypermethylation of residues in the undamaged DNA strand
- ○ E. Removal of deaminated bases by glycosylase

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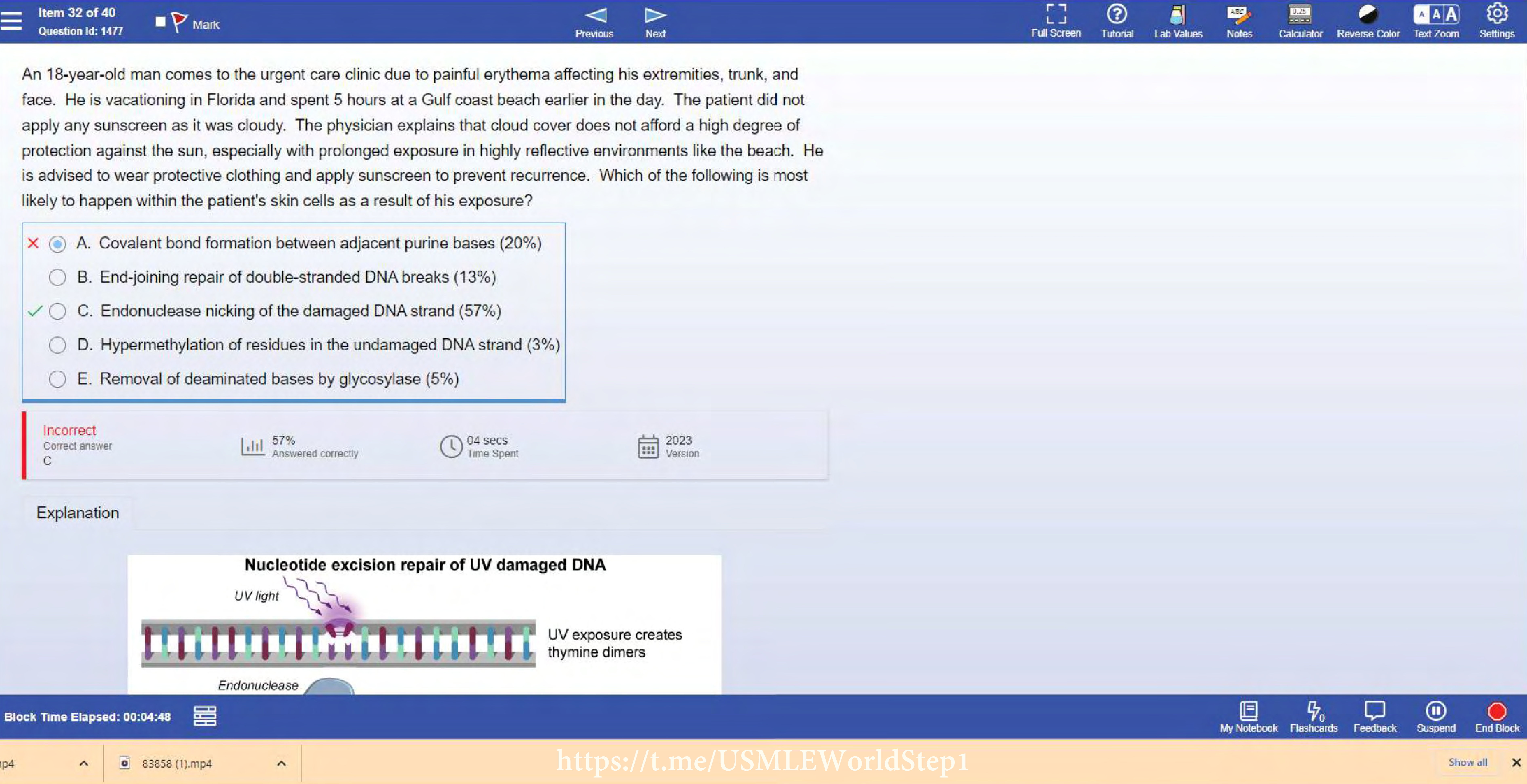
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 32 of 40
Question Id: 1477
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✗ ● A. Covalent bond formation between adjacent purine bases (20%)
- ○ B. End-joining repair of double-stranded DNA breaks (13%)
- ✓ ○ C. Endonuclease nicking of the damaged DNA strand (57%)
- ○ D. Hypermethylation of residues in the undamaged DNA strand (3%)
- ○ E. Removal of deaminated bases by glycosylase (5%)

Incorrect
Correct answer
C

57%
Answered correctly

04 secs
Time Spent

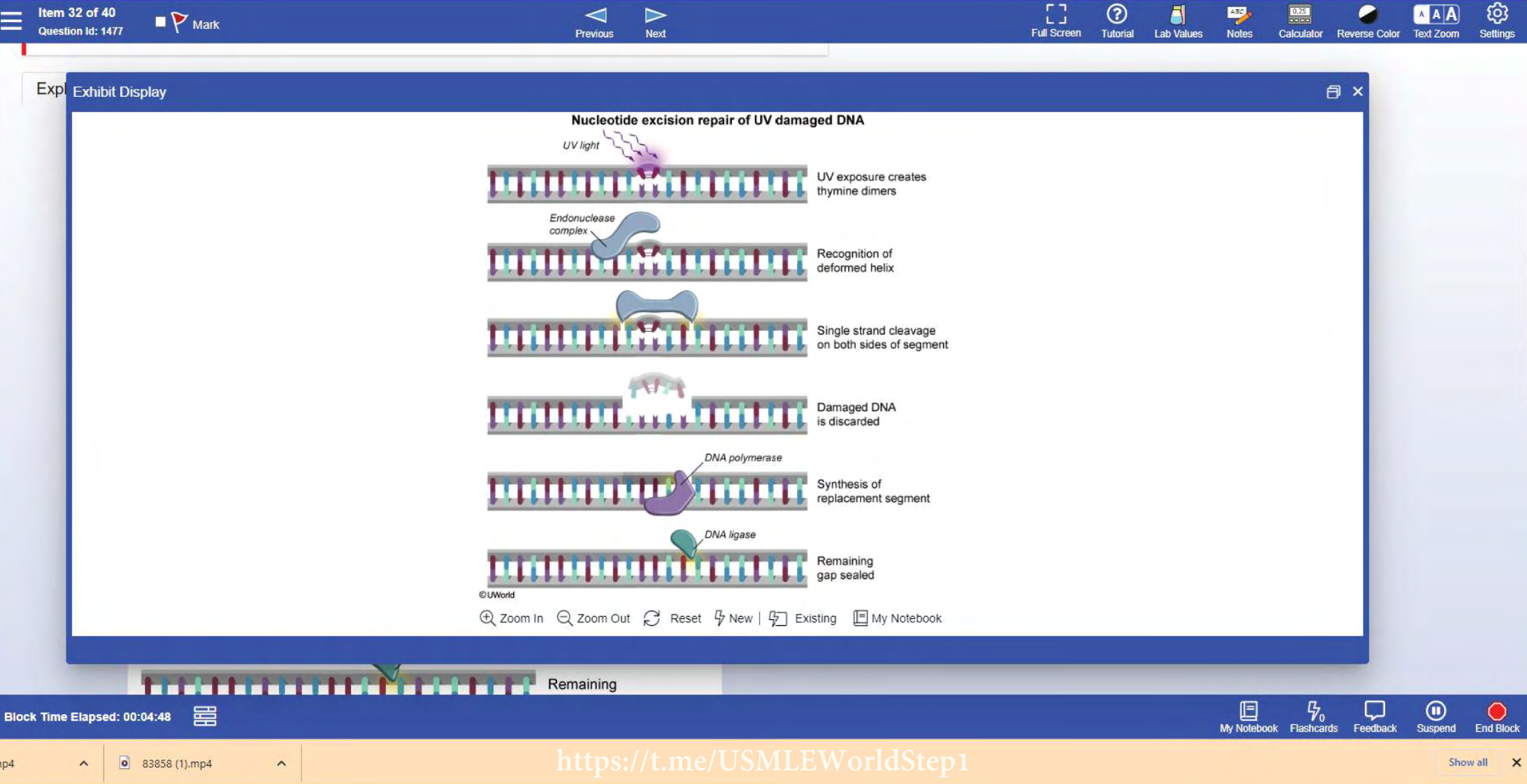
2023
Version

Explanation

Nucleotide excision repair of UV damaged DNA

UV light
UV exposure creates thymine dimers
Endonuclease

Block Time Elapsed: 00:04:48
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all


Item 32 of 40
Question Id: 1477
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display

Nucleotide excision repair of UV damaged DNA

UV light
UV exposure creates thymine dimers
Endonuclease complex
Recognition of deformed helix
Single strand cleavage on both sides of segment
Damaged DNA is discarded
DNA polymerase
Synthesis of replacement segment
DNA ligase
Remaining gap sealed
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New
Existing
My Notebook
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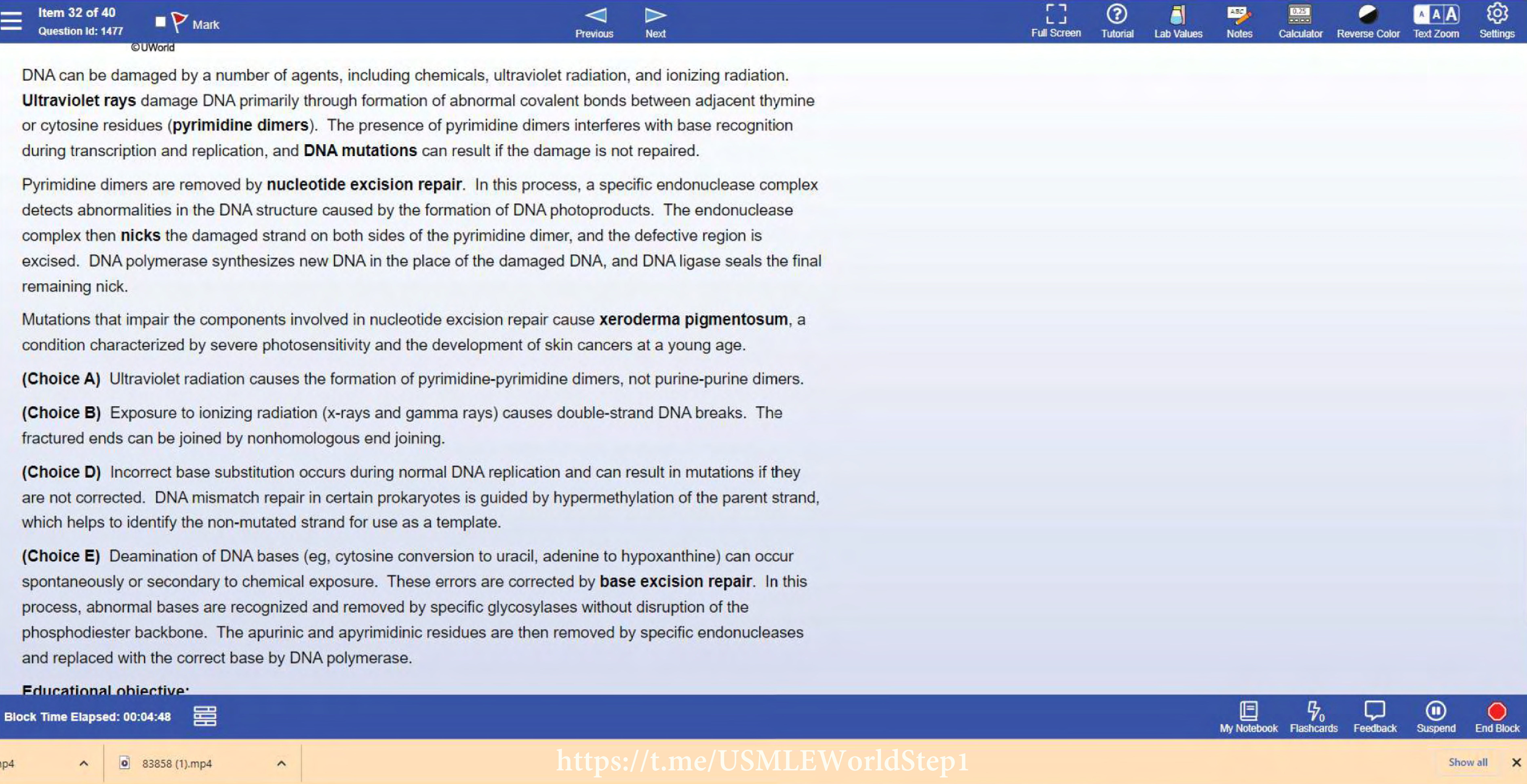
My Notebook
Flashcards
Feedback
Suspend
End Block
p4
83858 (1).mp4
Show all



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DNA can be damaged by a number of agents, including chemicals, ultraviolet radiation, and ionizing radiation. **Ultraviolet rays** damage DNA primarily through formation of abnormal covalent bonds between adjacent thymine or cytosine residues (**pyrimidine dimers**). The presence of pyrimidine dimers interferes with base recognition during transcription and replication, and **DNA mutations** can result if the damage is not repaired.

Pyrimidine dimers are removed by **nucleotide excision repair**. In this process, a specific endonuclease complex detects abnormalities in the DNA structure caused by the formation of DNA photoproducts. The endonuclease complex then **nicks** the damaged strand on both sides of the pyrimidine dimer, and the defective region is excised. DNA polymerase synthesizes new DNA in the place of the damaged DNA, and DNA ligase seals the final remaining nick.

Mutations that impair the components involved in nucleotide excision repair cause **xeroderma pigmentosum**, a condition characterized by severe photosensitivity and the development of skin cancers at a young age.

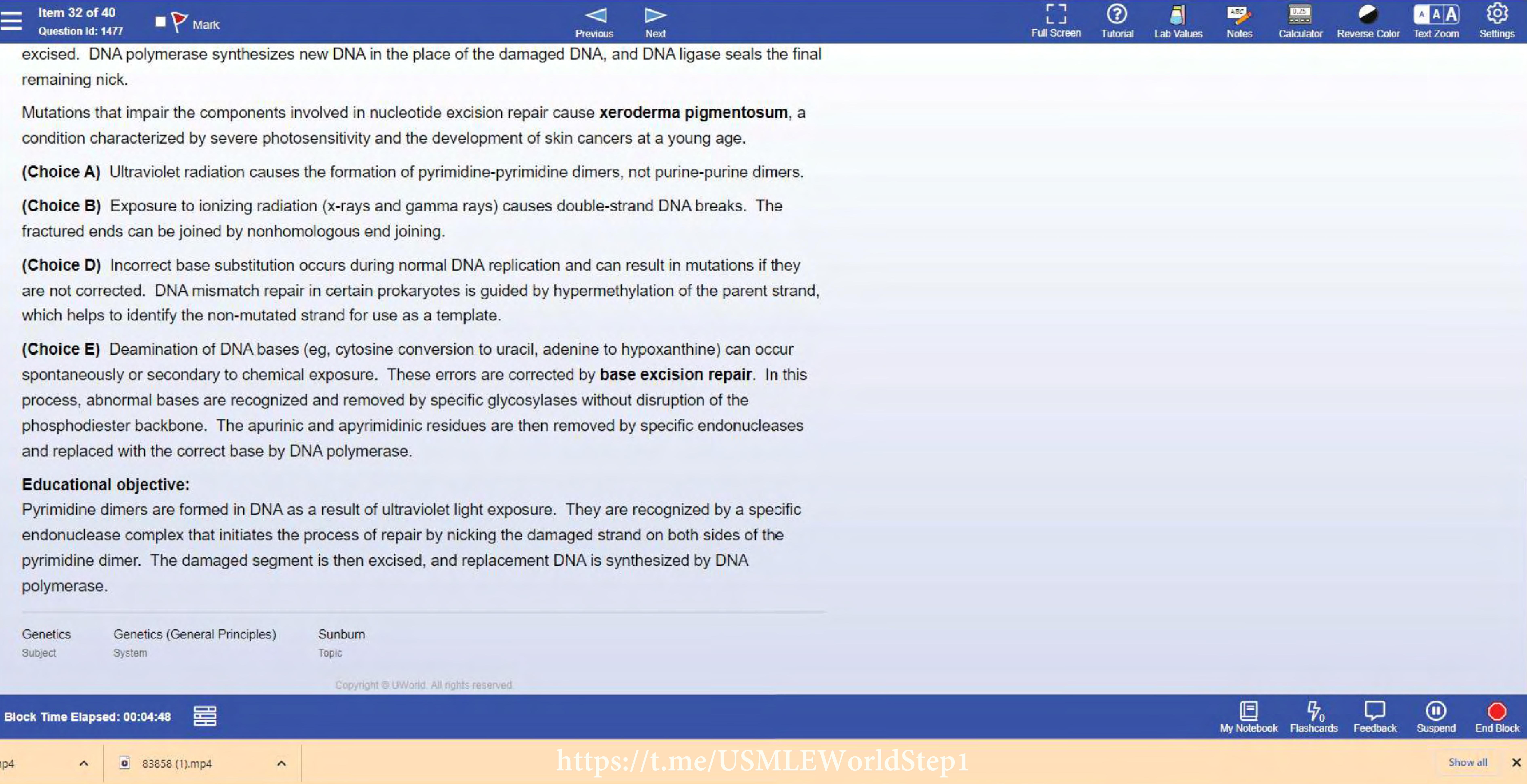
(Choice A) Ultraviolet radiation causes the formation of pyrimidine-pyrimidine dimers, not purine-purine dimers.

(Choice B) Exposure to ionizing radiation (x-rays and gamma rays) causes double-strand DNA breaks. The fractured ends can be joined by nonhomologous end joining.

(Choice D) Incorrect base substitution occurs during normal DNA replication and can result in mutations if they are not corrected. DNA mismatch repair in certain prokaryotes is guided by hypermethylation of the parent strand, which helps to identify the non-mutated strand for use as a template.

(Choice E) Deamination of DNA bases (eg, cytosine conversion to uracil, adenine to hypoxanthine) can occur spontaneously or secondary to chemical exposure. These errors are corrected by **base excision repair**. In this process, abnormal bases are recognized and removed by specific glycosylases without disruption of the phosphodiester backbone. The apurinic and apyrimidinic residues are then removed by specific endonucleases and replaced with the correct base by DNA polymerase.

Educational objective:


Item 32 of 40
Question Id: 1477
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

excised. DNA polymerase synthesizes new DNA in the place of the damaged DNA, and DNA ligase seals the final remaining nick.

Mutations that impair the components involved in nucleotide excision repair cause **xeroderma pigmentosum**, a condition characterized by severe photosensitivity and the development of skin cancers at a young age.

(Choice A) Ultraviolet radiation causes the formation of pyrimidine-pyrimidine dimers, not purine-purine dimers.

(Choice B) Exposure to ionizing radiation (x-rays and gamma rays) causes double-strand DNA breaks. The fractured ends can be joined by nonhomologous end joining.

(Choice D) Incorrect base substitution occurs during normal DNA replication and can result in mutations if they are not corrected. DNA mismatch repair in certain prokaryotes is guided by hypermethylation of the parent strand, which helps to identify the non-mutated strand for use as a template.

(Choice E) Deamination of DNA bases (eg, cytosine conversion to uracil, adenine to hypoxanthine) can occur spontaneously or secondary to chemical exposure. These errors are corrected by **base excision repair**. In this process, abnormal bases are recognized and removed by specific glycosylases without disruption of the phosphodiester backbone. The apurinic and apyrimidinic residues are then removed by specific endonucleases and replaced with the correct base by DNA polymerase.

Educational objective:

Pyrimidine dimers are formed in DNA as a result of ultraviolet light exposure. They are recognized by a specific endonuclease complex that initiates the process of repair by nicking the damaged strand on both sides of the pyrimidine dimer. The damaged segment is then excised, and replacement DNA is synthesized by DNA polymerase.

Genetics
Subject

Genetics (General Principles)
System

Sunburn
Topic

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Feedback
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End Block
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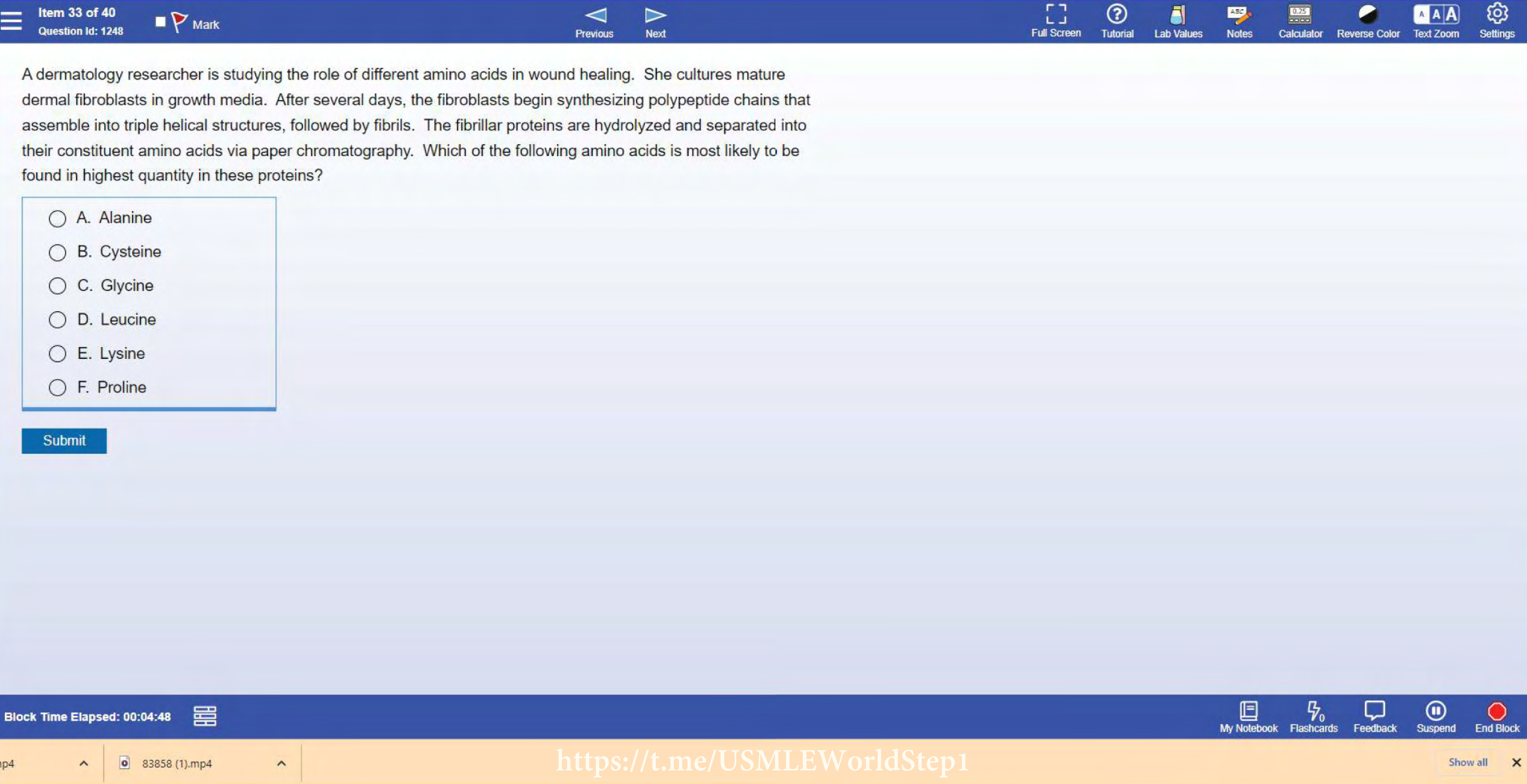
Show all


Item 33 of 40
Question Id: 1248
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A dermatology researcher is studying the role of different amino acids in wound healing. She cultures mature dermal fibroblasts in growth media. After several days, the fibroblasts begin synthesizing polypeptide chains that assemble into triple helical structures, followed by fibrils. The fibrillar proteins are hydrolyzed and separated into their constituent amino acids via paper chromatography. Which of the following amino acids is most likely to be found in highest quantity in these proteins?

○ A. Alanine
○ B. Cysteine
○ C. Glycine
○ D. Leucine
○ E. Lysine
○ F. Proline

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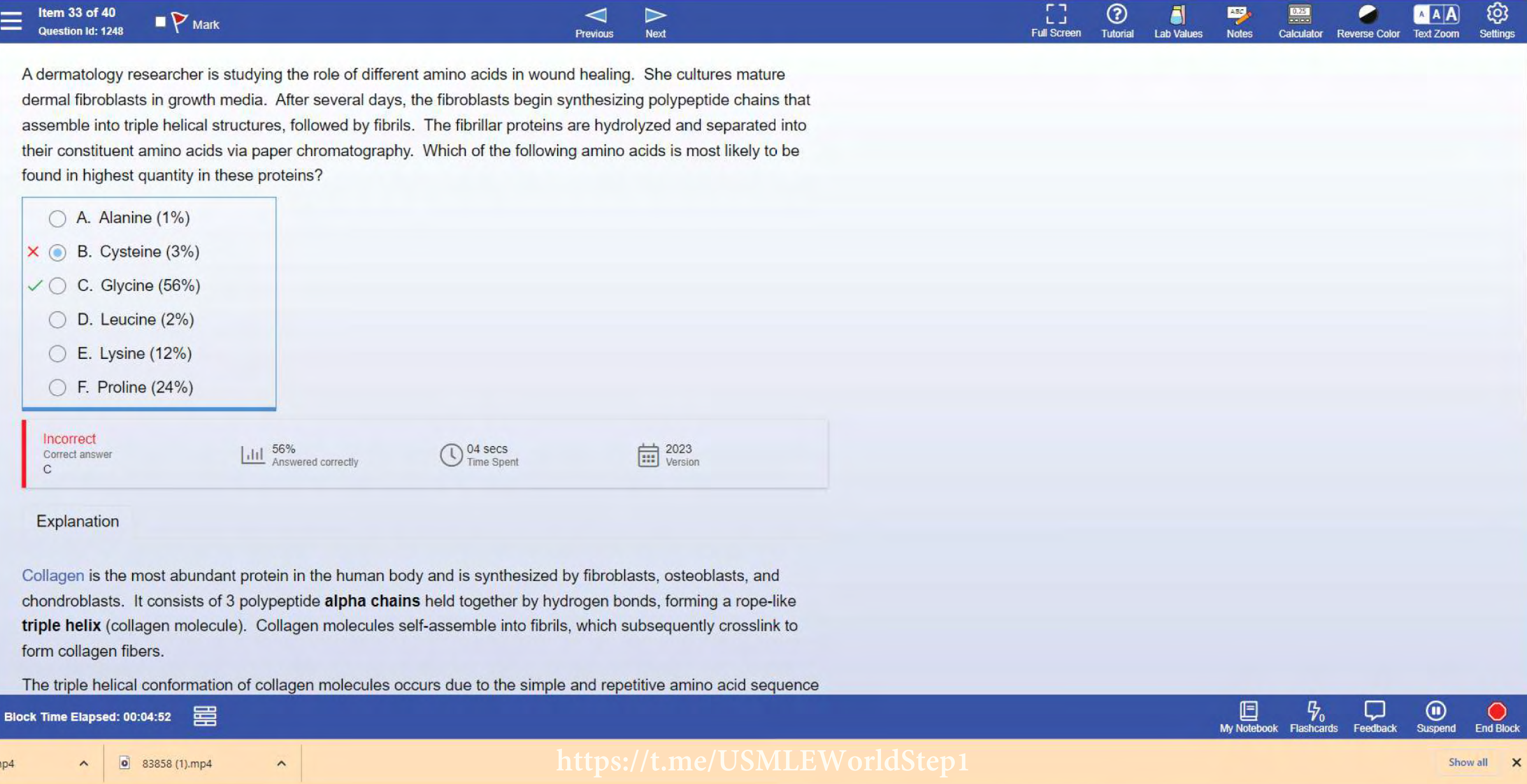
Item 33 of 40
Question Id: 1248
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:52
My Notebook
Flashcards
Feedback
Suspend
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A dermatology researcher is studying the role of different amino acids in wound healing. She cultures mature dermal fibroblasts in growth media. After several days, the fibroblasts begin synthesizing polypeptide chains that assemble into triple helical structures, followed by fibrils. The fibrillar proteins are hydrolyzed and separated into their constituent amino acids via paper chromatography. Which of the following amino acids is most likely to be found in highest quantity in these proteins?

- ○ A. Alanine (1%)
- ✗ ● B. Cysteine (3%)
- ✓ ○ C. Glycine (56%)
- ○ D. Leucine (2%)
- ○ E. Lysine (12%)
- ○ F. Proline (24%)

Incorrect
Correct answer
C

56%
Answered correctly

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2023
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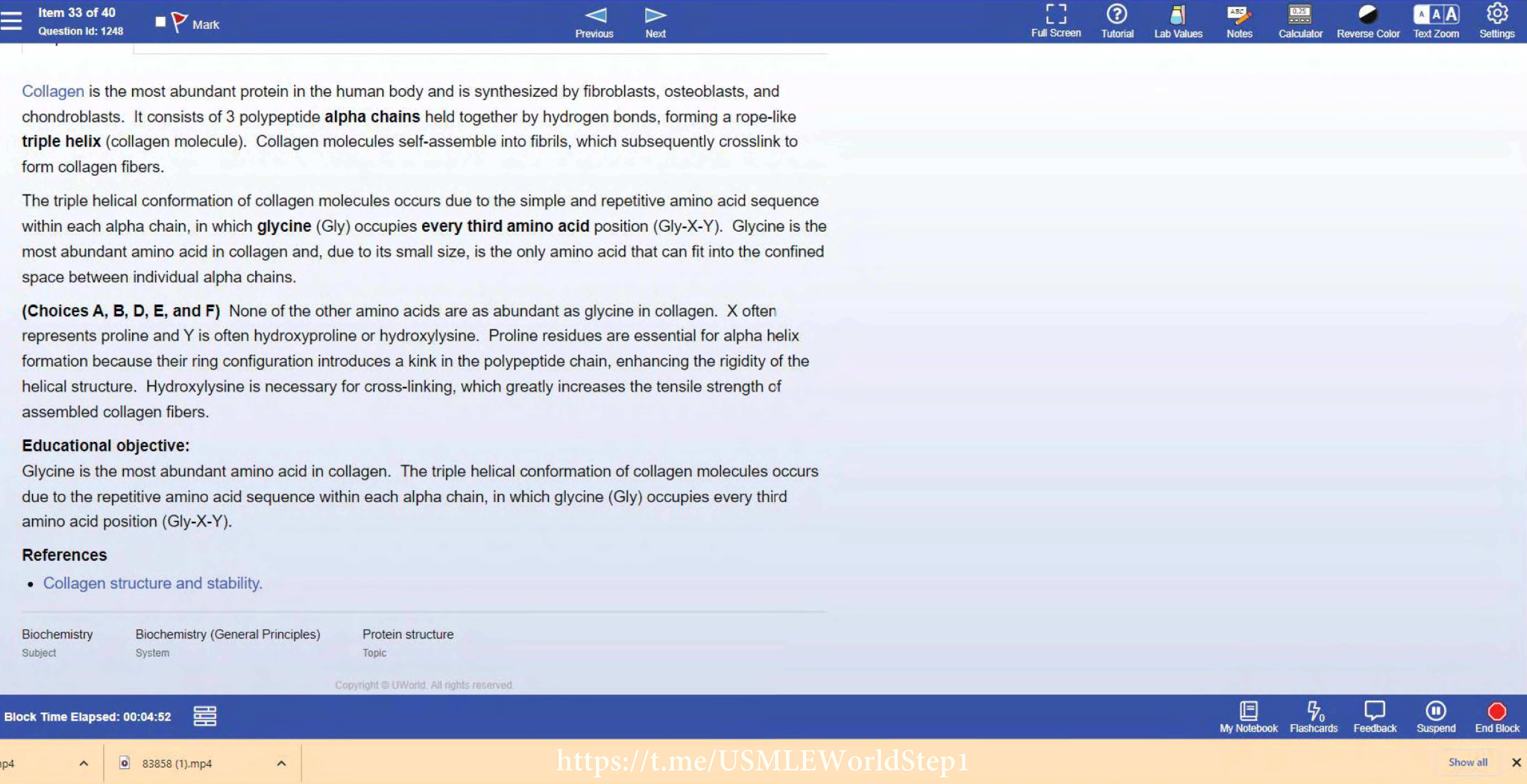
Explanation

Collagen is the most abundant protein in the human body and is synthesized by fibroblasts, osteoblasts, and chondroblasts. It consists of 3 polypeptide **alpha chains** held together by hydrogen bonds, forming a rope-like **triple helix** (collagen molecule). Collagen molecules self-assemble into fibrils, which subsequently crosslink to form collagen fibers.

The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence


Item 33 of 40
Question Id: 1248
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Collagen is the most abundant protein in the human body and is synthesized by fibroblasts, osteoblasts, and chondroblasts. It consists of 3 polypeptide **alpha chains** held together by hydrogen bonds, forming a rope-like **triple helix** (collagen molecule). Collagen molecules self-assemble into fibrils, which subsequently crosslink to form collagen fibers.

The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence within each alpha chain, in which **glycine** (Gly) occupies **every third amino acid** position (Gly-X-Y). Glycine is the most abundant amino acid in collagen and, due to its small size, is the only amino acid that can fit into the confined space between individual alpha chains.

(Choices A, B, D, E, and F) None of the other amino acids are as abundant as glycine in collagen. X often represents proline and Y is often hydroxyproline or hydroxylysine. Proline residues are essential for alpha helix formation because their ring configuration introduces a kink in the polypeptide chain, enhancing the rigidity of the helical structure. Hydroxylysine is necessary for cross-linking, which greatly increases the tensile strength of assembled collagen fibers.

Educational objective:
Glycine is the most abundant amino acid in collagen. The triple helical conformation of collagen molecules occurs due to the repetitive amino acid sequence within each alpha chain, in which glycine (Gly) occupies every third amino acid position (Gly-X-Y).

References

- Collagen structure and stability.

Biochemistry	Biochemistry (General Principles)	Protein structure
Subject	System	Topic

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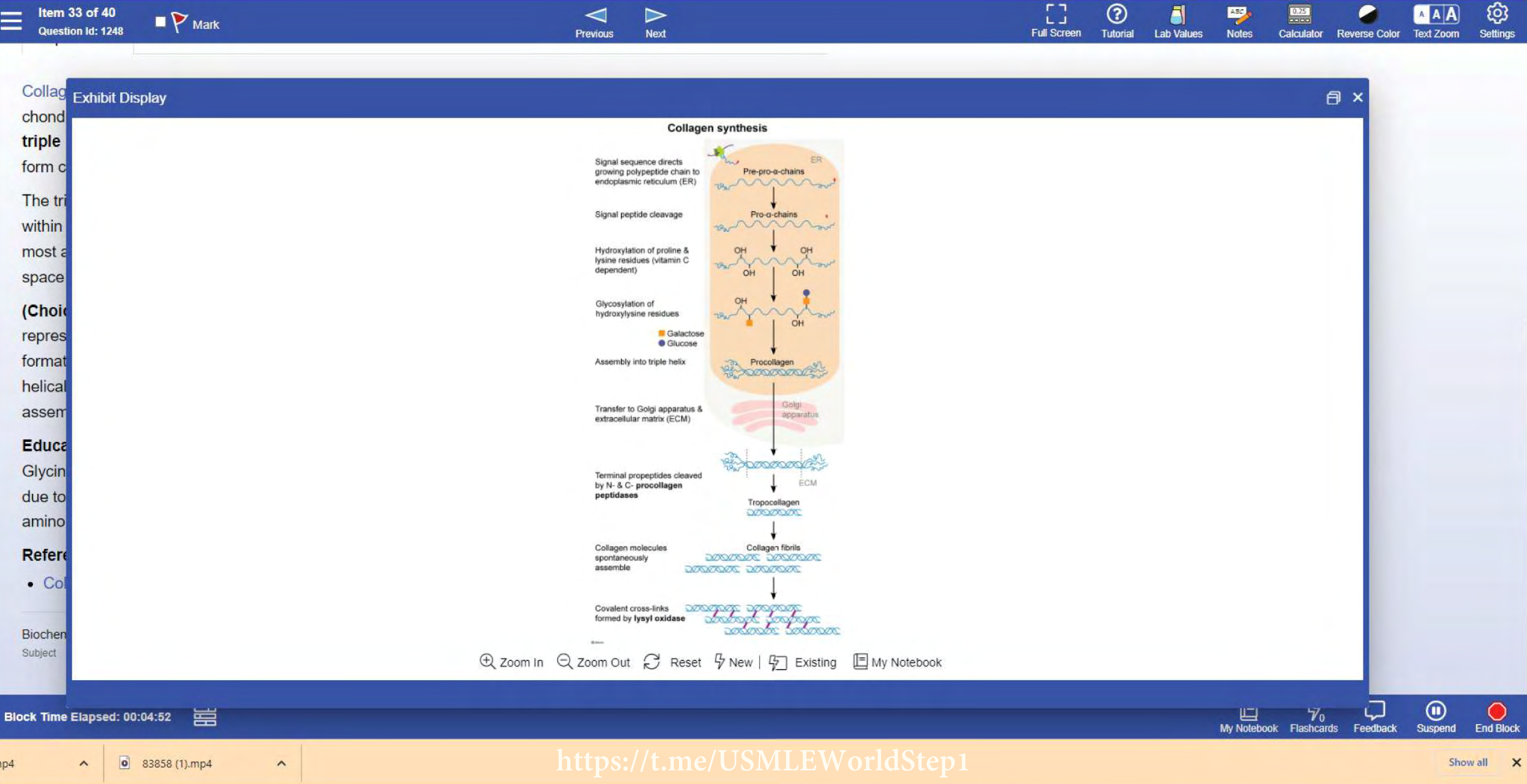
Item 33 of 40
Question Id: 1248
Mark
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Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Biochem
Subject

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Collagen synthesis

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Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)
Pre-pro-α-chains
Signal peptide cleavage
Pro-α-chains
Hydroxylation of proline & lysine residues (vitamin C dependent)
OH
OH
OH
OH
Glycosylation of hydroxylysine residues
OH
OH
🟧 Galactose
● Glucose
Assembly into triple helix
Procollagen
Transfer to Golgi apparatus & extracellular matrix (ECM)
Golgi apparatus
Terminal propeptides cleaved by N- & C- **procollagen peptidases**
ECM
Tropocollagen
Collagen molecules spontaneously assemble
Collagen fibrils
Covalent cross-links formed by **lysyl oxidase**

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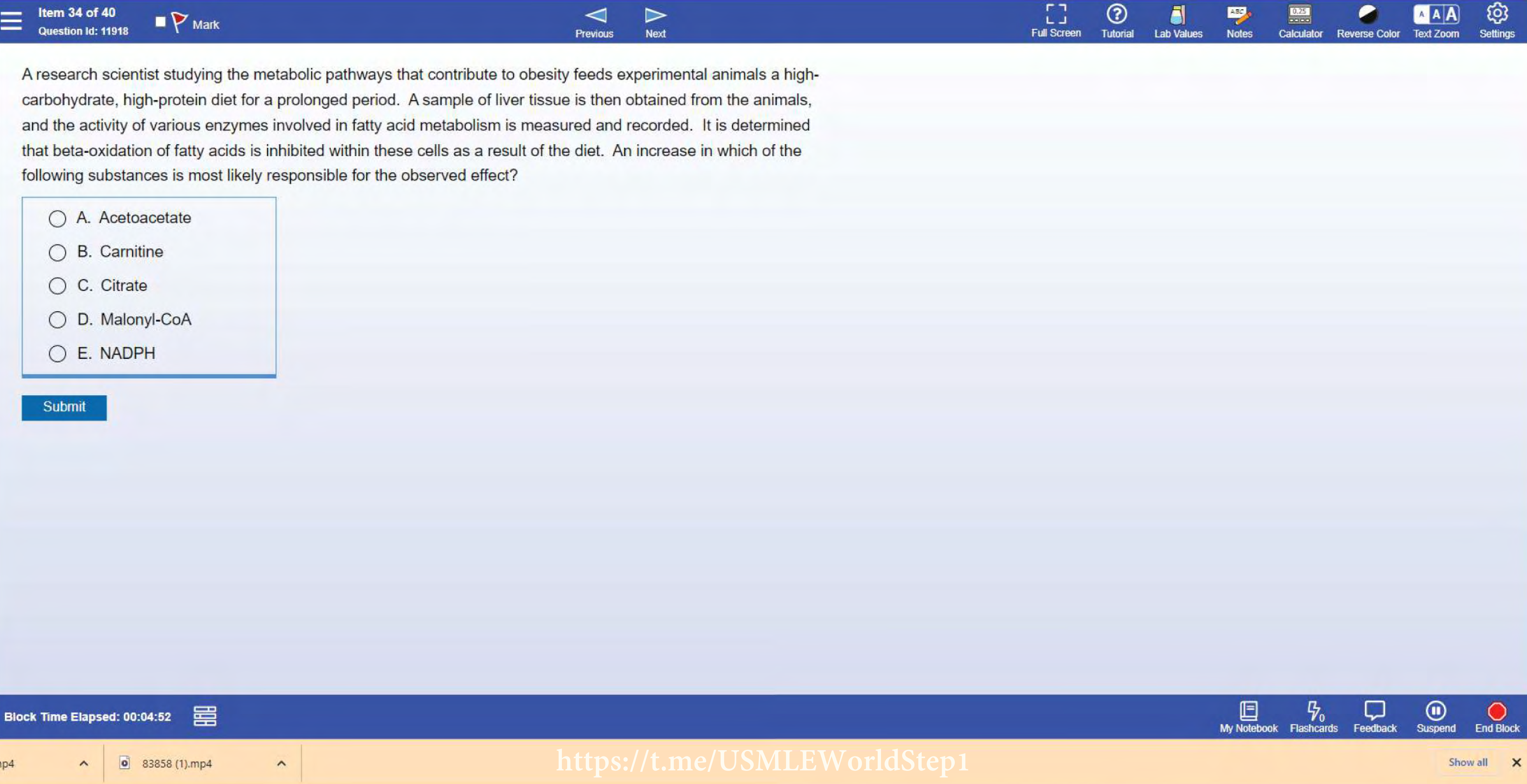
Item 34 of 40
Question Id: 11918
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

○ A. Acetoacetate
○ B. Carnitine
○ C. Citrate
○ D. Malonyl-CoA
○ E. NADPH

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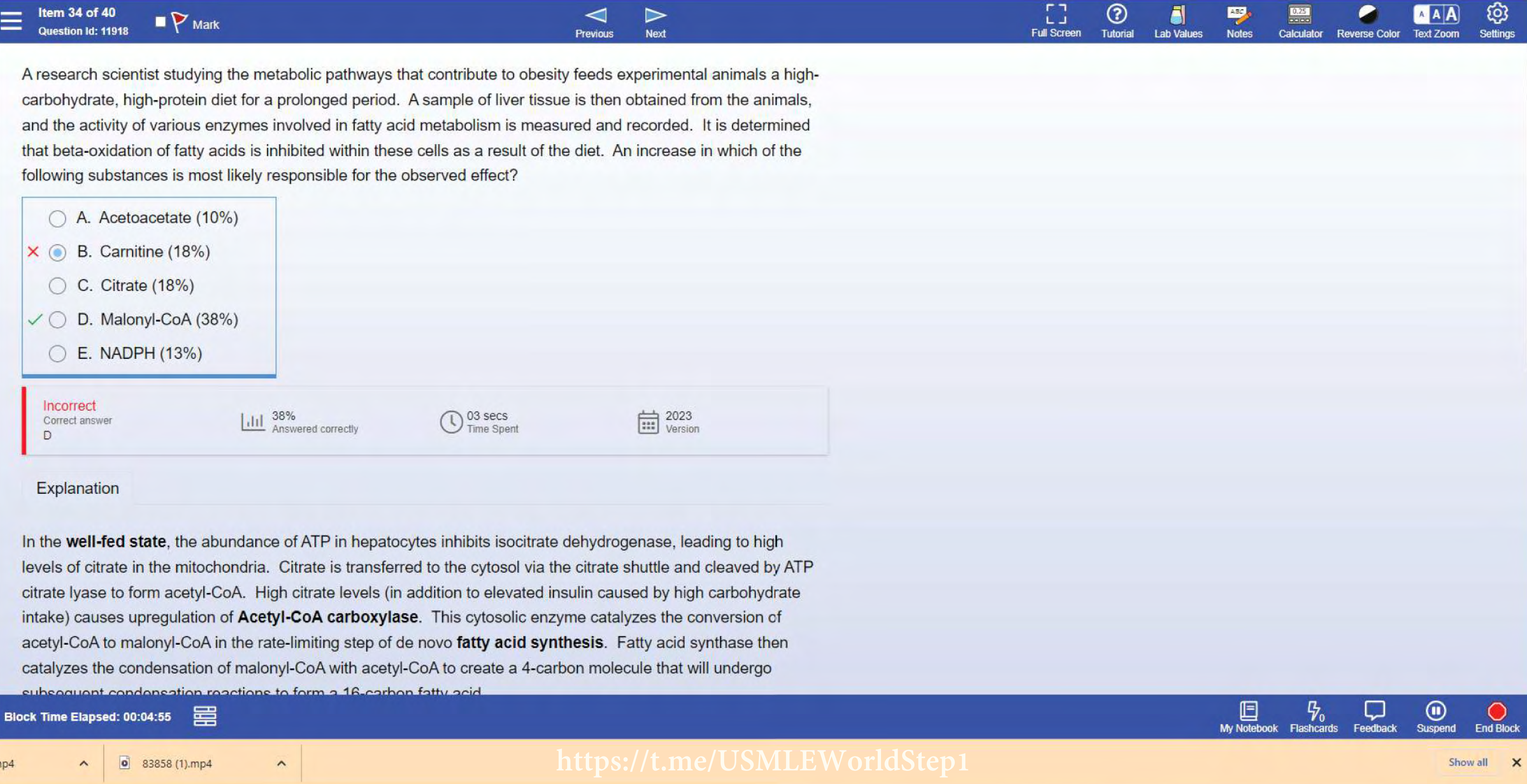
Item 34 of 40
Question Id: 11918
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ A. Acetoacetate (10%)
- ✗ ● B. Carnitine (18%)
- ○ C. Citrate (18%)
- ✓ ○ D. Malonyl-CoA (38%)
- ○ E. NADPH (13%)

Incorrect
Correct answer
D

38%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

In the **well-fed state**, the abundance of ATP in hepatocytes inhibits isocitrate dehydrogenase, leading to high levels of citrate in the mitochondria. Citrate is transferred to the cytosol via the citrate shuttle and cleaved by ATP citrate lyase to form acetyl-CoA. High citrate levels (in addition to elevated insulin caused by high carbohydrate intake) causes upregulation of **Acetyl-CoA carboxylase**. This cytosolic enzyme catalyzes the conversion of acetyl-CoA to malonyl-CoA in the rate-limiting step of de novo **fatty acid synthesis**. Fatty acid synthase then catalyzes the condensation of malonyl-CoA with acetyl-CoA to create a 4-carbon molecule that will undergo subsequent condensation reactions to form a 16-carbon fatty acid

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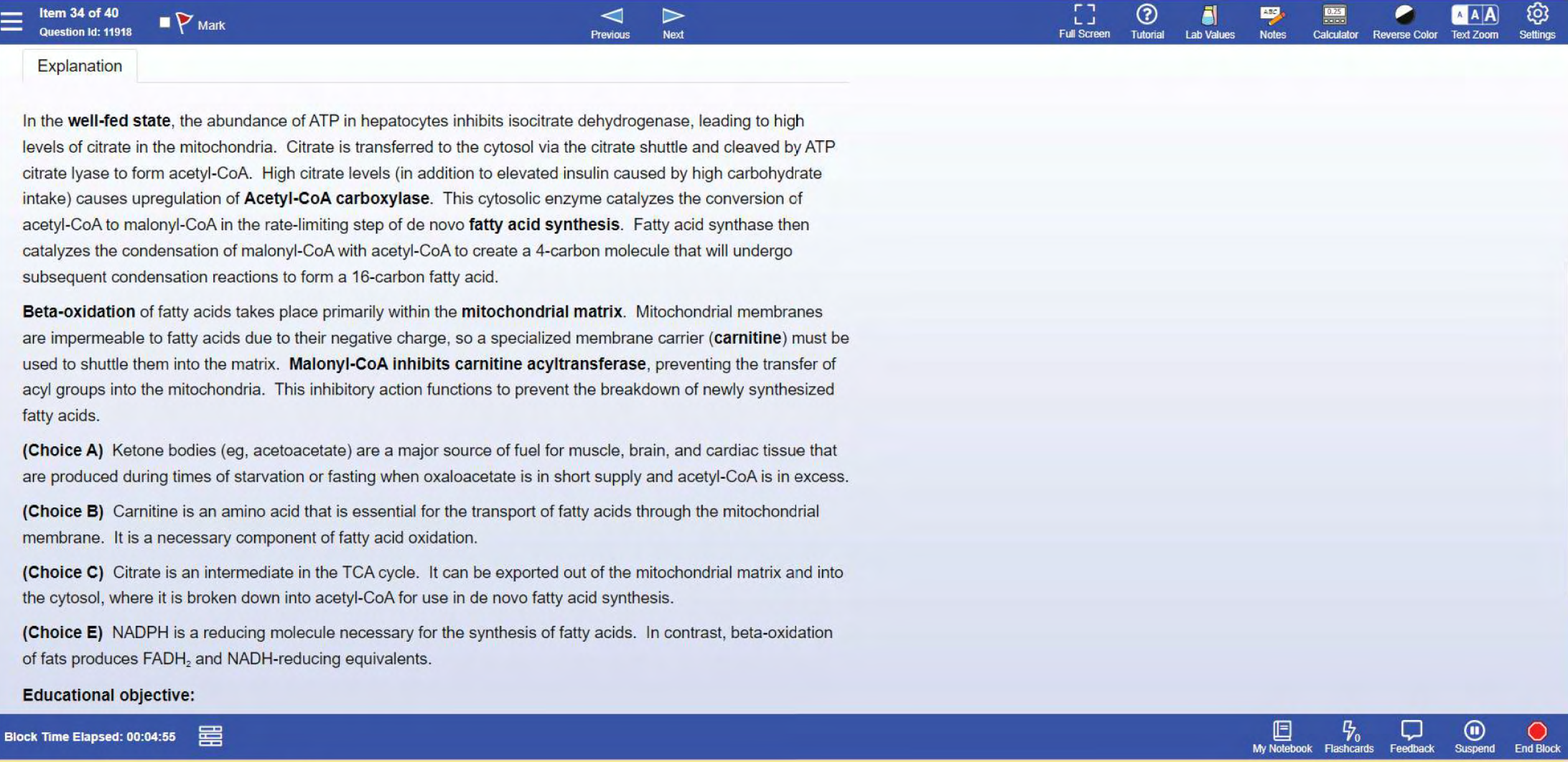

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Beta-oxidation of fatty acids takes place primarily within the **mitochondrial matrix**. Mitochondrial membranes are impermeable to fatty acids due to their negative charge, so a specialized membrane carrier (**carnitine**) must be used to shuttle them into the matrix. **Malonyl-CoA inhibits carnitine acyltransferase**, preventing the transfer of acyl groups into the mitochondria. This inhibitory action functions to prevent the breakdown of newly synthesized fatty acids.

(Choice A) Ketone bodies (eg, acetoacetate) are a major source of fuel for muscle, brain, and cardiac tissue that are produced during times of starvation or fasting when oxaloacetate is in short supply and acetyl-CoA is in excess.

(Choice B) Carnitine is an amino acid that is essential for the transport of fatty acids through the mitochondrial membrane. It is a necessary component of fatty acid oxidation.

(Choice C) Citrate is an intermediate in the TCA cycle. It can be exported out of the mitochondrial matrix and into the cytosol, where it is broken down into acetyl-CoA for use in de novo fatty acid synthesis.

(Choice E) NADPH is a reducing molecule necessary for the synthesis of fatty acids. In contrast, beta-oxidation of fats produces $FADH_2$ and NADH-reducing equivalents.

Educational objective:

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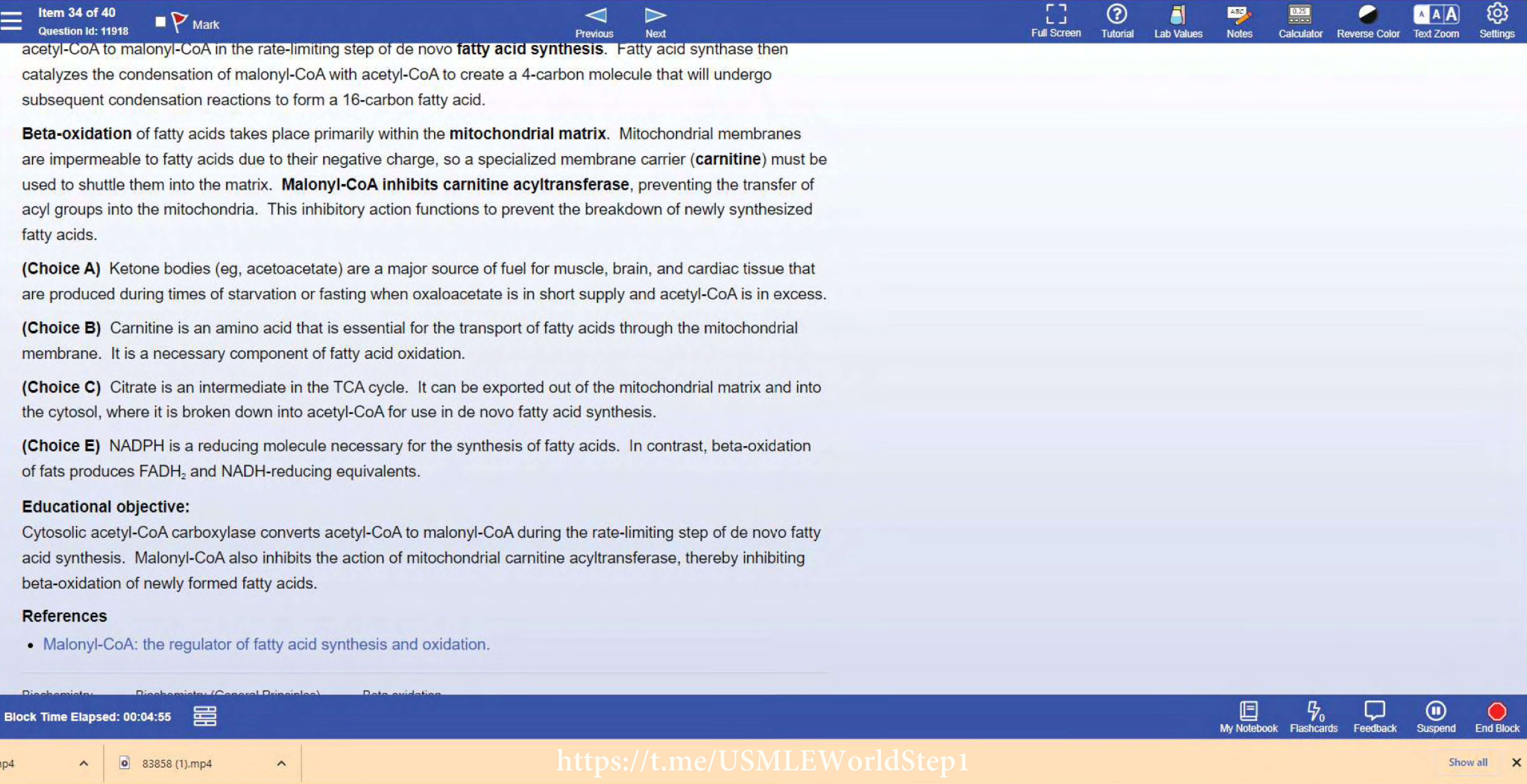
Item 34 of 40
Question Id: 11918
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:04:55
My Notebook
Flashcards
Feedback
Suspend
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(Choice E) NADPH is a reducing molecule necessary for the synthesis of fatty acids. In contrast, beta-oxidation of fats produces $FADH_2$ and NADH-reducing equivalents.

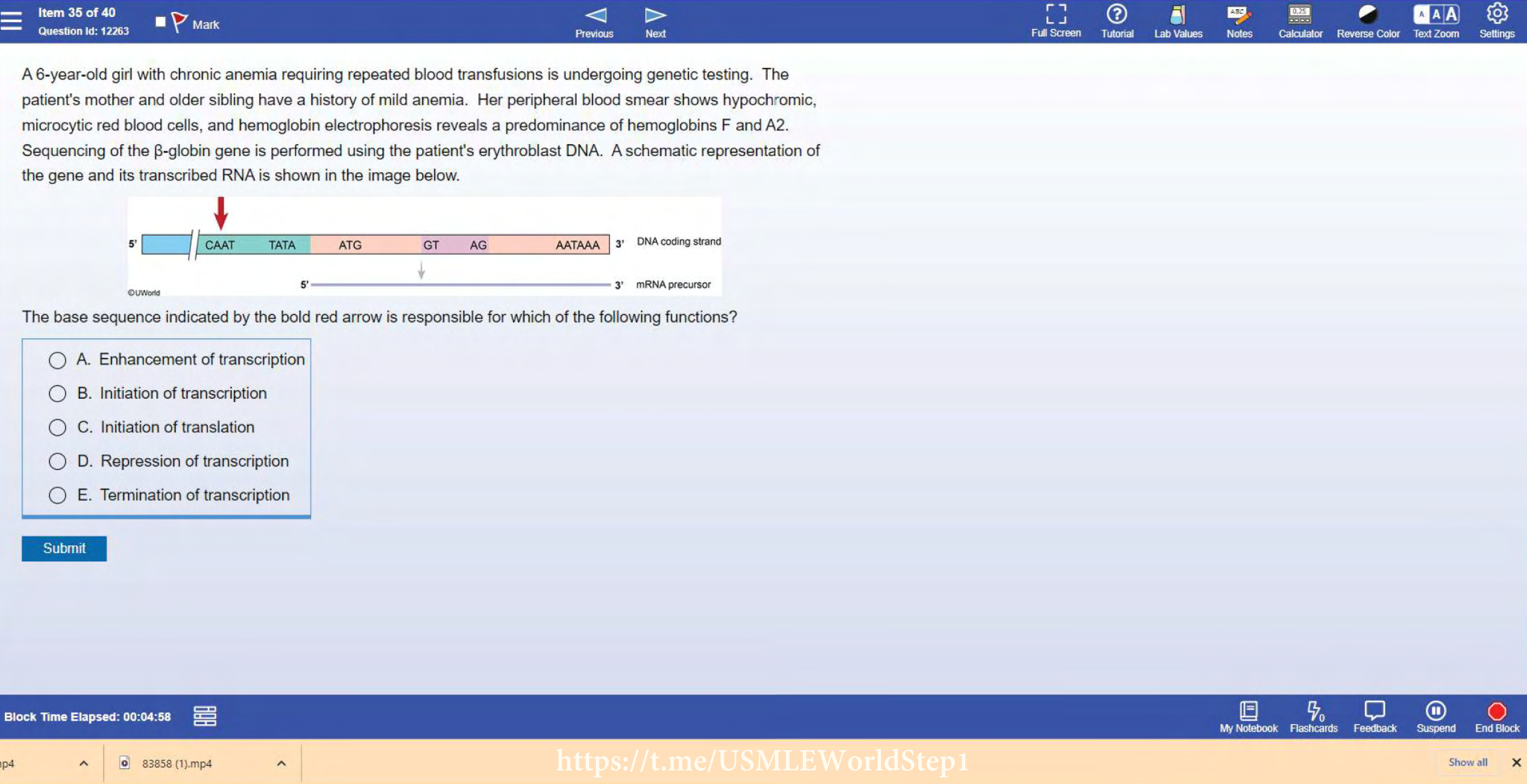
Educational objective:

Cytosolic acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA during the rate-limiting step of de novo fatty acid synthesis. Malonyl-CoA also inhibits the action of mitochondrial carnitine acyltransferase, thereby inhibiting beta-oxidation of newly formed fatty acids.

References

- Malonyl-CoA: the regulator of fatty acid synthesis and oxidation.

Biochemistry Biochemistry (General Principles) Beta-oxidation


Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 6-year-old girl with chronic anemia requiring repeated blood transfusions is undergoing genetic testing. The patient's mother and older sibling have a history of mild anemia. Her peripheral blood smear shows hypochromic, microcytic red blood cells, and hemoglobin electrophoresis reveals a predominance of hemoglobins F and A2. Sequencing of the β-globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.

5'
CAAT
TATA
ATG
GT
AG
AATAAA
3'
DNA coding strand
5'
3'
mRNA precursor
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The base sequence indicated by the bold red arrow is responsible for which of the following functions?

○ A. Enhancement of transcription
○ B. Initiation of transcription
○ C. Initiation of translation
○ D. Repression of transcription
○ E. Termination of transcription

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Feedback
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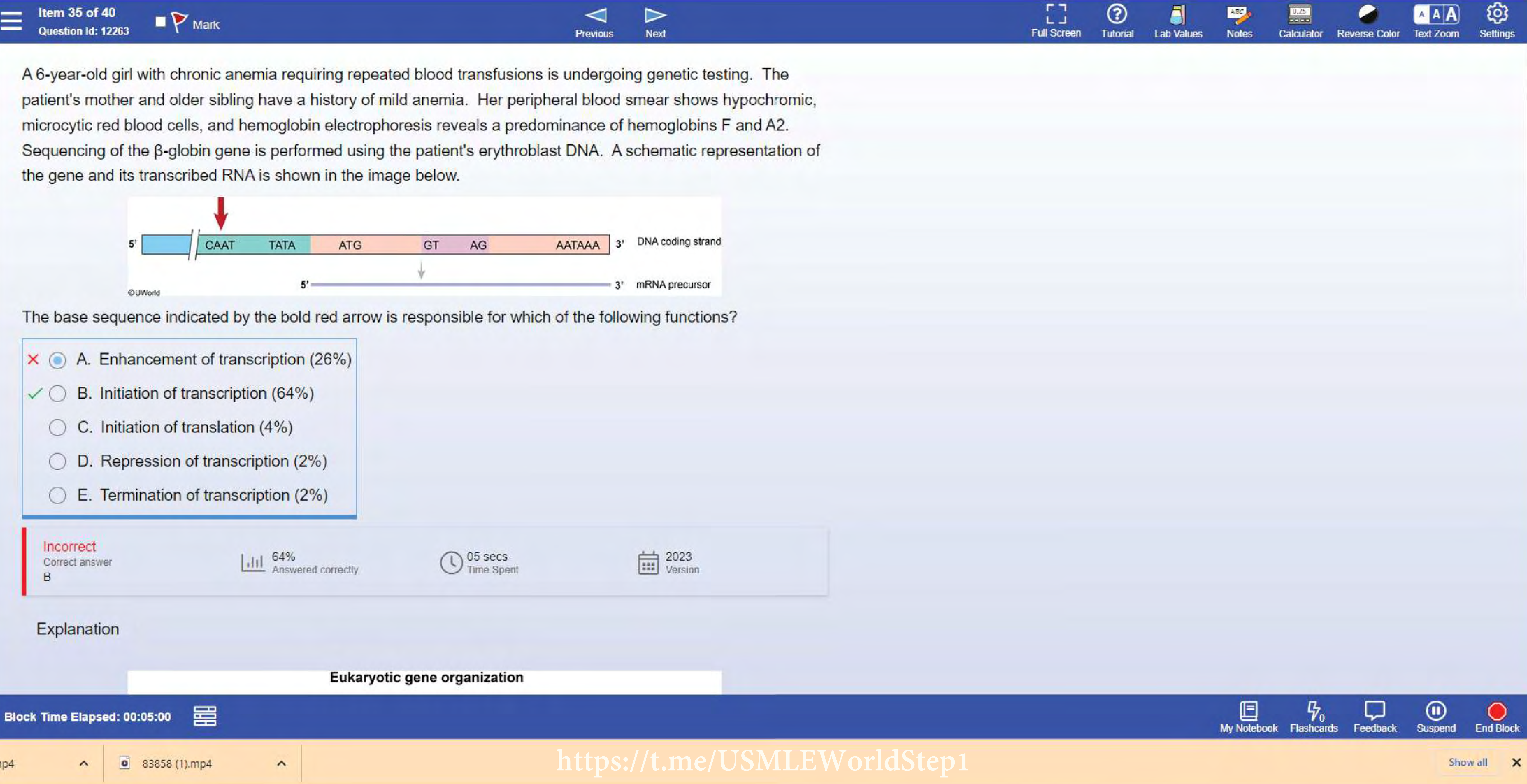
Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 6-year-old girl with chronic anemia requiring repeated blood transfusions is undergoing genetic testing. The patient's mother and older sibling have a history of mild anemia. Her peripheral blood smear shows hypochromic, microcytic red blood cells, and hemoglobin electrophoresis reveals a predominance of hemoglobins F and A2. Sequencing of the β-globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.

5'
CAAT
TATA
ATG
GT
AG
AATAAA
3'
DNA coding strand
5'
3'
mRNA precursor
©UWorld

The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- ✗ ● A. Enhancement of transcription (26%)
- ✓ ○ B. Initiation of transcription (64%)
- ○ C. Initiation of translation (4%)
- ○ D. Repression of transcription (2%)
- ○ E. Termination of transcription (2%)

Incorrect
Correct answer
B

64%
Answered correctly

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2023
Version

Explanation

Eukaryotic gene organization

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My Notebook
Flashcards
Feedback
Suspend
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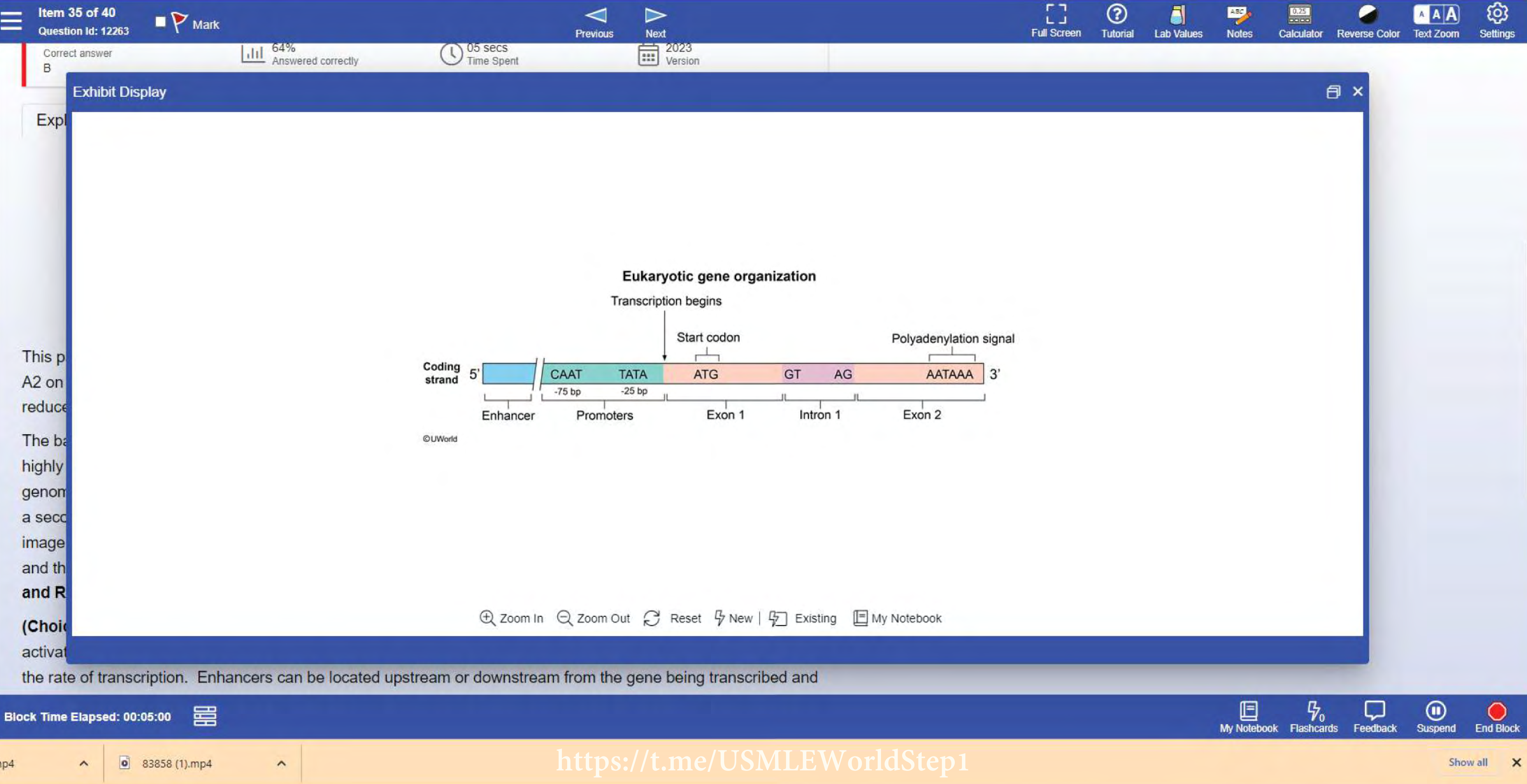

Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:05:00
My Notebook
Flashcards
Feedback
Suspend
End Block
83858 (1).mp4
Show all

Correct answer
B

64%
Answered correctly

05 secs
Time Spent

2023
Version

Expl

Eukaryotic gene organization

Transcription begins
Start codon
Polyadenylation signal
Coding strand
5'
CAAT
TATA
ATG
GT
AG
AATAAA
3'
-75 bp
-25 bp
Enhancer
Promoters
Exon 1
Intron 1
Exon 2

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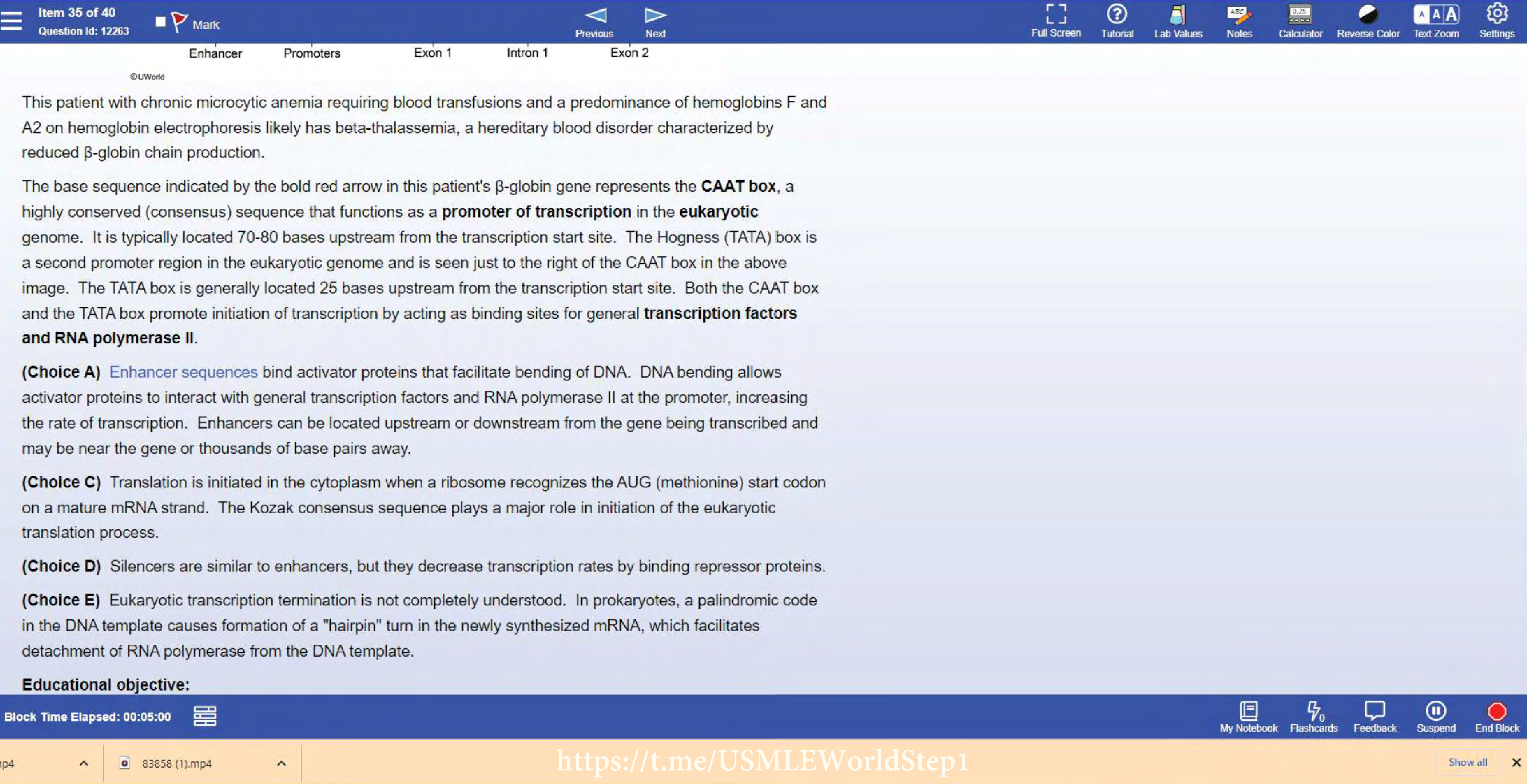
Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Exon 1
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Block Time Elapsed: 00:05:00
My Notebook
Flashcards
Feedback
Suspend
End Block
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This patient with chronic microcytic anemia requiring blood transfusions and a predominance of hemoglobins F and A2 on hemoglobin electrophoresis likely has beta-thalassemia, a hereditary blood disorder characterized by reduced β-globin chain production.

The base sequence indicated by the bold red arrow in this patient's β-globin gene represents the **CAAT box**, a highly conserved (consensus) sequence that functions as a **promoter of transcription** in the **eukaryotic** genome. It is typically located 70-80 bases upstream from the transcription start site. The Hogness (TATA) box is a second promoter region in the eukaryotic genome and is seen just to the right of the CAAT box in the above image. The TATA box is generally located 25 bases upstream from the transcription start site. Both the CAAT box and the TATA box promote initiation of transcription by acting as binding sites for general **transcription factors and RNA polymerase II**.

(Choice A) Enhancer sequences bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the rate of transcription. Enhancers can be located upstream or downstream from the gene being transcribed and may be near the gene or thousands of base pairs away.

(Choice C) Translation is initiated in the cytoplasm when a ribosome recognizes the AUG (methionine) start codon on a mature mRNA strand. The Kozak consensus sequence plays a major role in initiation of the eukaryotic translation process.

(Choice D) Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

(Choice E) Eukaryotic transcription termination is not completely understood. In prokaryotes, a palindromic code in the DNA template causes formation of a "hairpin" turn in the newly synthesized mRNA, which facilitates detachment of RNA polymerase from the DNA template.

Educational objective:

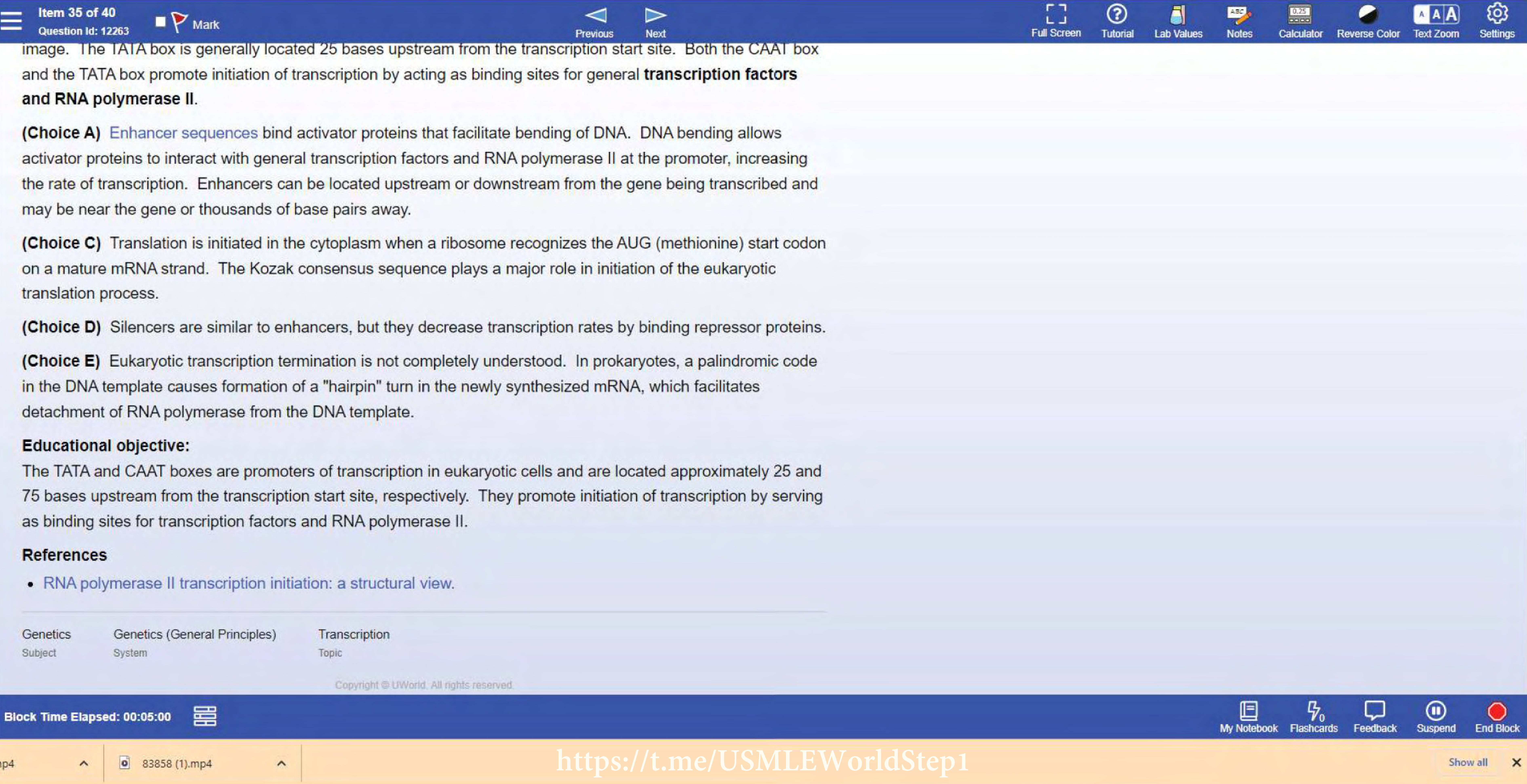
Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

image. The TATA box is generally located 25 bases upstream from the transcription start site. Both the CAAT box and the TATA box promote initiation of transcription by acting as binding sites for general **transcription factors and RNA polymerase II**.

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Educational objective:

The TATA and CAAT boxes are promoters of transcription in eukaryotic cells and are located approximately 25 and 75 bases upstream from the transcription start site, respectively. They promote initiation of transcription by serving as binding sites for transcription factors and RNA polymerase II.

References

- RNA polymerase II transcription initiation: a structural view.

Genetics	Genetics (General Principles)	Transcription
Subject	System	Topic

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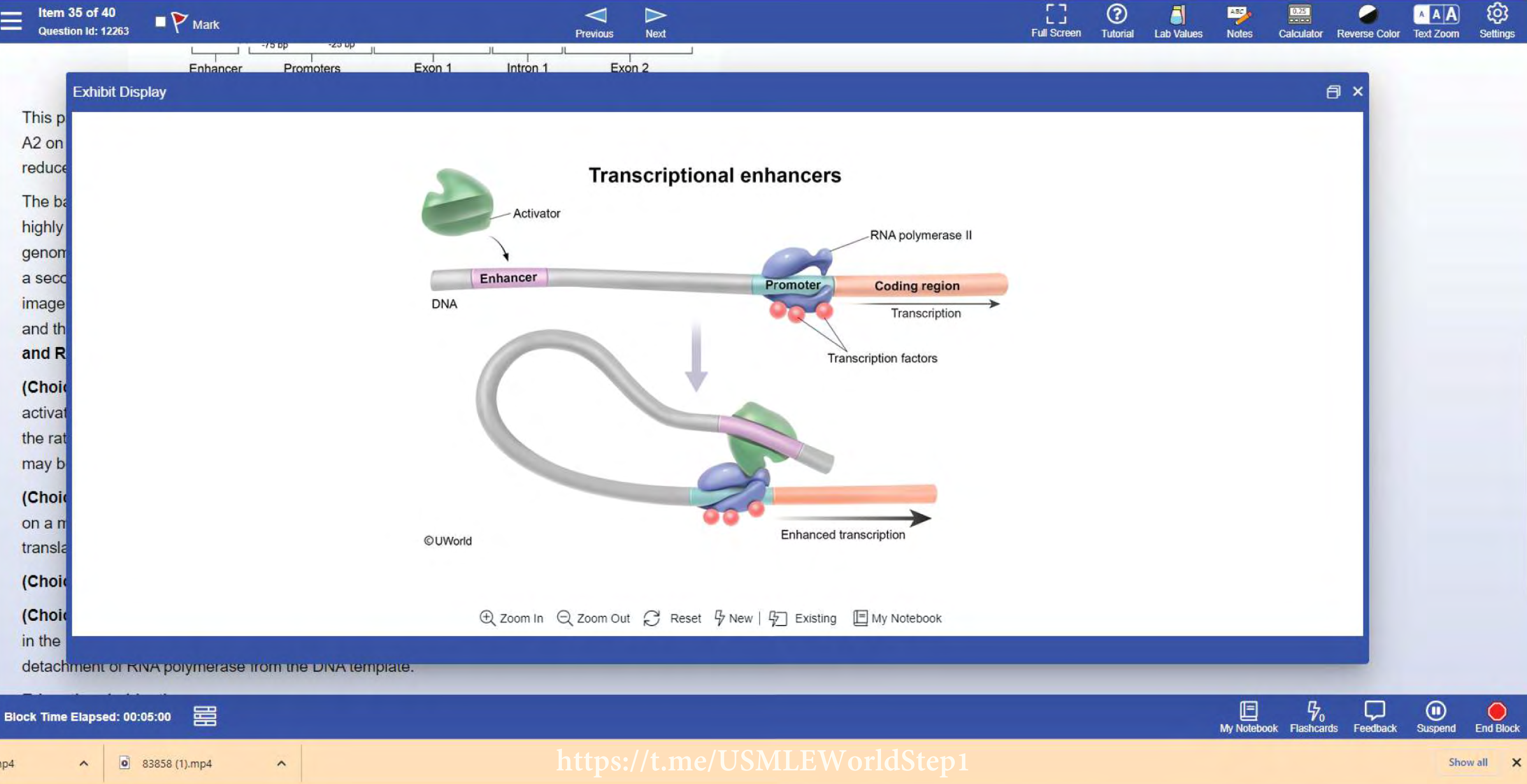

Item 35 of 40
Question Id: 12263
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Activator
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Promoter
Coding region
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New
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My Notebook
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Feedback
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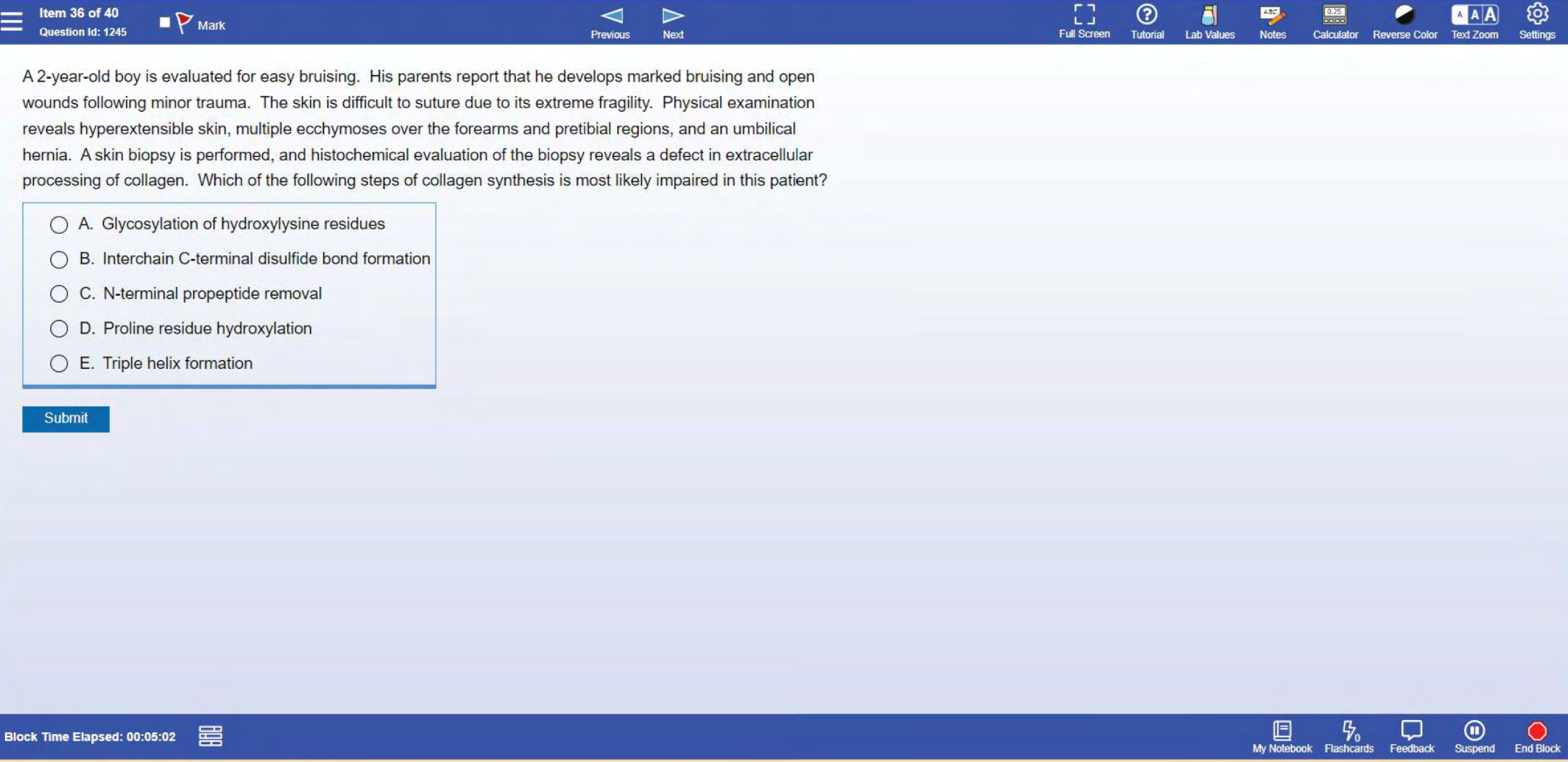
Item 36 of 40
Question Id: 1245
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:05:02
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Flashcards
Feedback
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A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

○ A. Glycosylation of hydroxylysine residues
○ B. Interchain C-terminal disulfide bond formation
○ C. N-terminal propeptide removal
○ D. Proline residue hydroxylation
○ E. Triple helix formation

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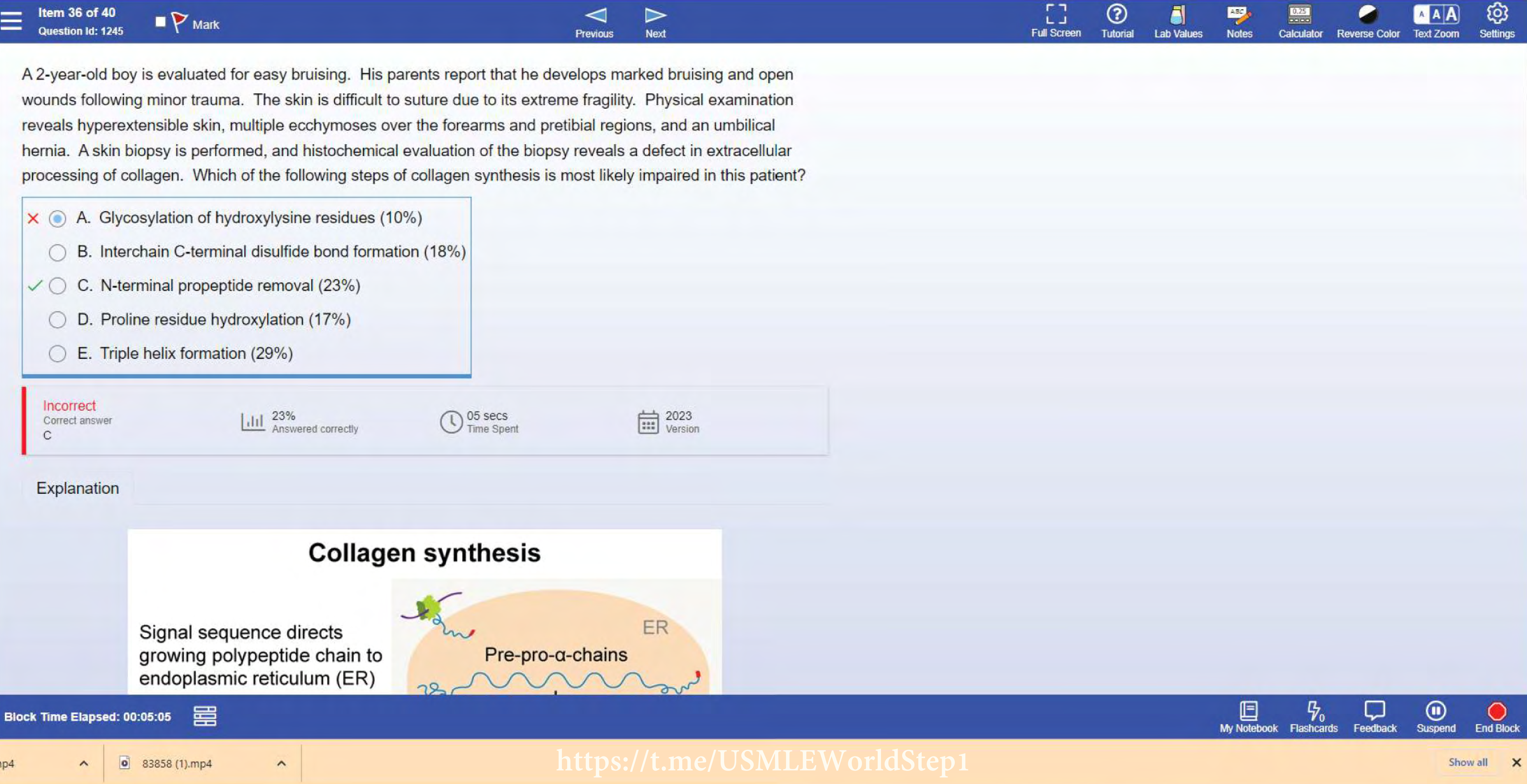

Item 36 of 40
Question Id: 1245
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

✗ ● A. Glycosylation of hydroxylysine residues (10%)

○ B. Interchain C-terminal disulfide bond formation (18%)

✓ ○ C. N-terminal propeptide removal (23%)

○ D. Proline residue hydroxylation (17%)

○ E. Triple helix formation (29%)

Incorrect
Correct answer
C

23%
Answered correctly

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Time Spent

2023
Version

Explanation

Collagen synthesis

Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)

ER
Pre-pro-α-chains
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My Notebook
Flashcards
Feedback
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End Block
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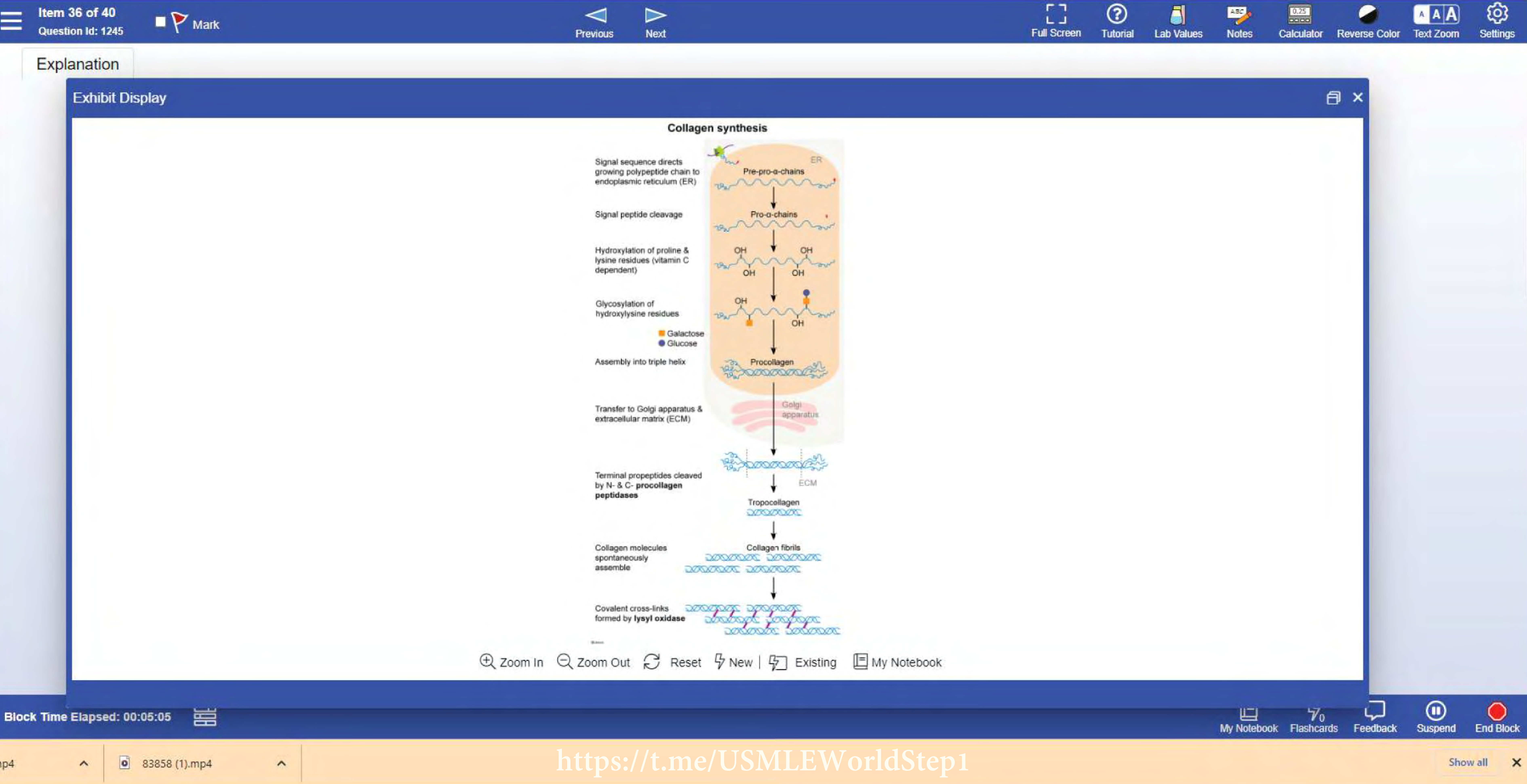
Item 36 of 40
Question Id: 1245
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display

Collagen synthesis

Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)

Signal peptide cleavage

Hydroxylation of proline & lysine residues (vitamin C dependent)

Glycosylation of hydroxylysine residues

- ■ Galactose
- ● Glucose

Assembly into triple helix

Transfer to Golgi apparatus & extracellular matrix (ECM)

Terminal propeptides cleaved by N- & C- **procollagen peptidases**

Collagen molecules spontaneously assemble

Covalent cross-links formed by **lysyl oxidase**

ER
Pre-pro-α-chains
Pro-α-chains
OH
OH
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OH
OH
OH
Procollagen
Golgi apparatus
ECM
Tropocollagen
Collagen fibrils
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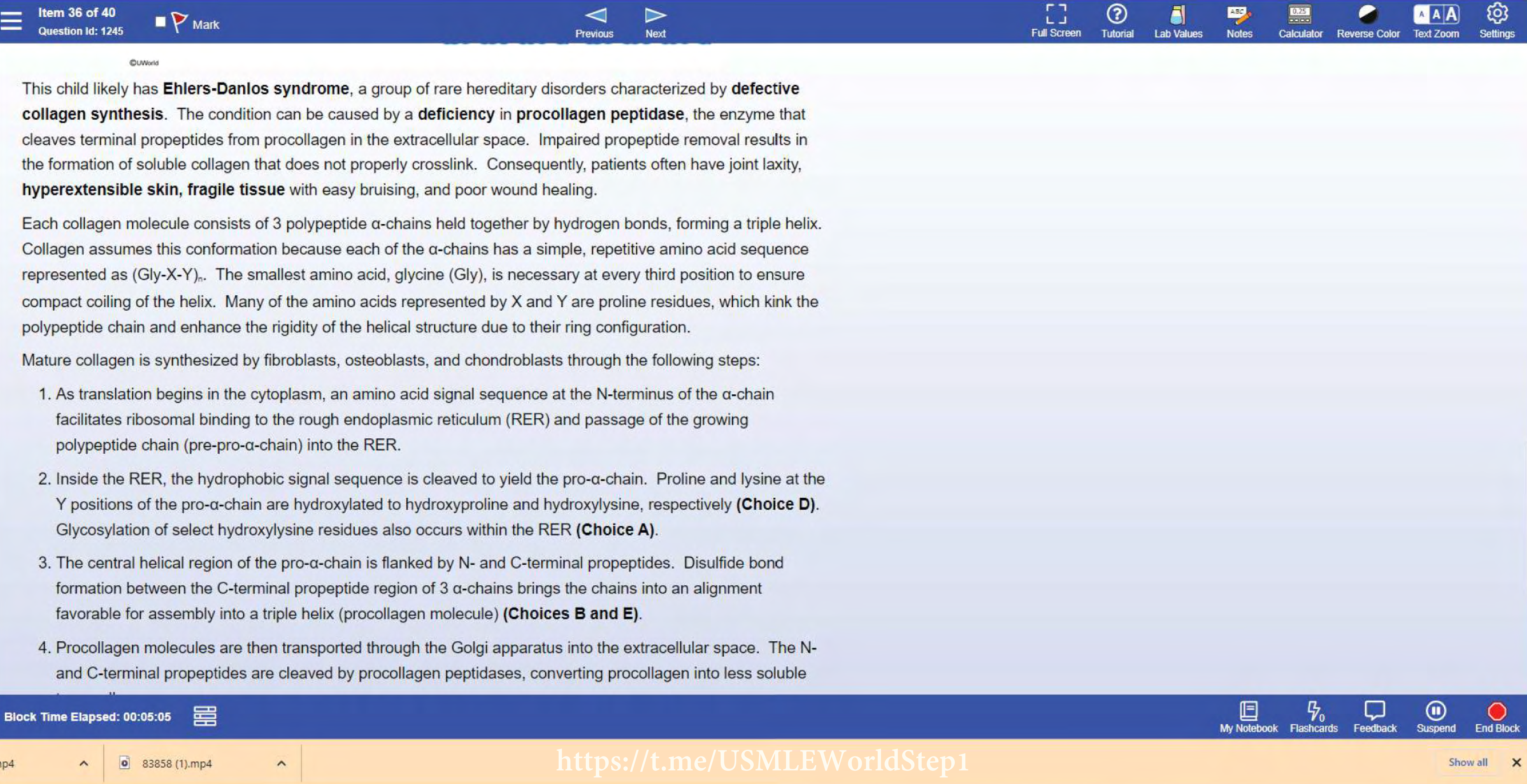
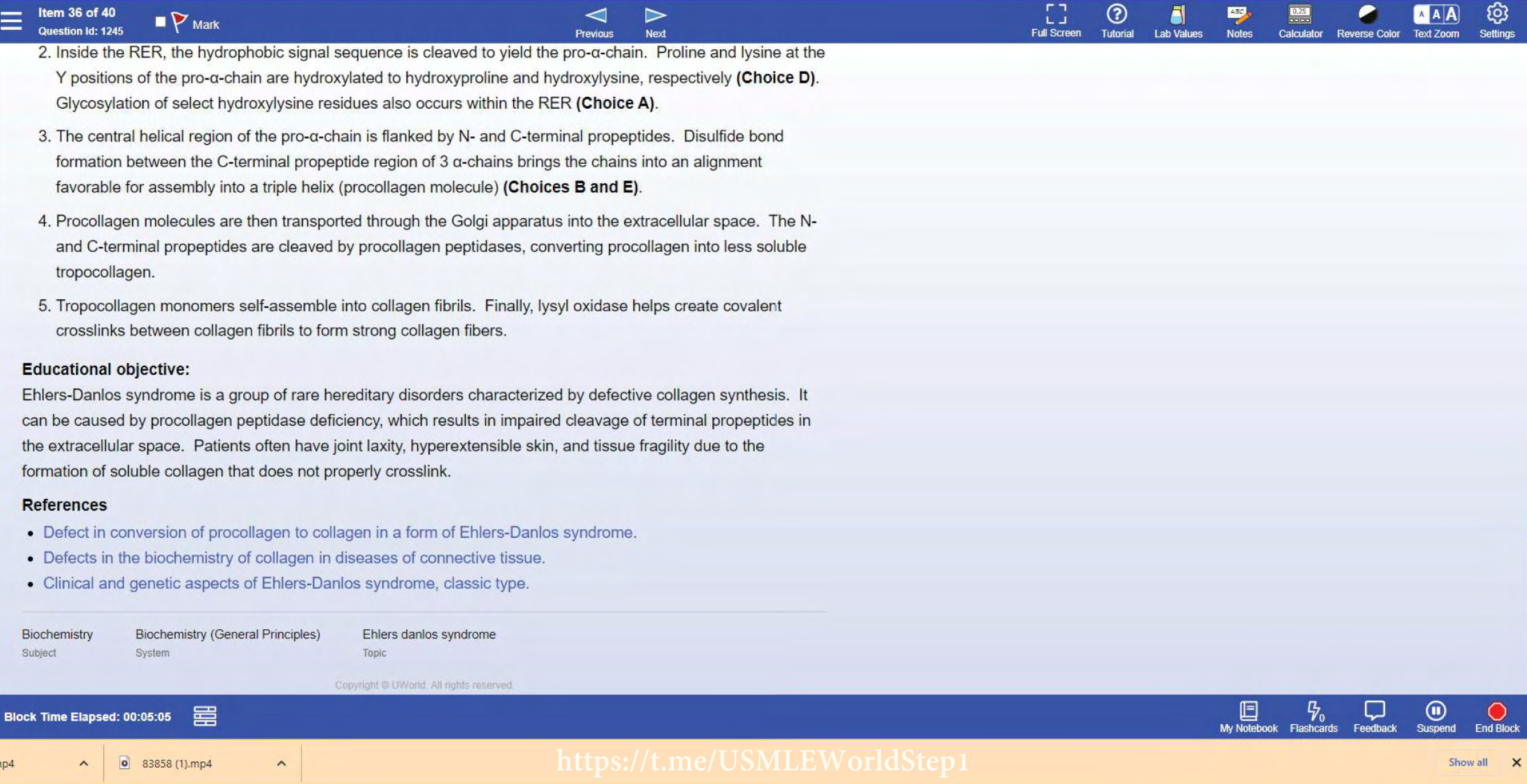


This child likely has **Ehlers-Danlos syndrome**, a group of rare hereditary disorders characterized by **defective collagen synthesis**. The condition can be caused by a **deficiency** in **procollagen peptidase**, the enzyme that cleaves terminal propeptides from procollagen in the extracellular space. Impaired propeptide removal results in the formation of soluble collagen that does not properly crosslink. Consequently, patients often have joint laxity, **hyperextensible skin, fragile tissue** with easy bruising, and poor wound healing.

Each collagen molecule consists of 3 polypeptide α-chains held together by hydrogen bonds, forming a triple helix. Collagen assumes this conformation because each of the α-chains has a simple, repetitive amino acid sequence represented as (Gly-X-Y)$_n$. The smallest amino acid, glycine (Gly), is necessary at every third position to ensure compact coiling of the helix. Many of the amino acids represented by X and Y are proline residues, which kink the polypeptide chain and enhance the rigidity of the helical structure due to their ring configuration.

Mature collagen is synthesized by fibroblasts, osteoblasts, and chondroblasts through the following steps:

1. As translation begins in the cytoplasm, an amino acid signal sequence at the N-terminus of the α-chain facilitates ribosomal binding to the rough endoplasmic reticulum (RER) and passage of the growing polypeptide chain (pre-pro-α-chain) into the RER.
2. Inside the RER, the hydrophobic signal sequence is cleaved to yield the pro-α-chain. Proline and lysine at the Y positions of the pro-α-chain are hydroxylated to hydroxyproline and hydroxylysine, respectively **(Choice D)**. Glycosylation of select hydroxylysine residues also occurs within the RER **(Choice A)**.
3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.
4. Procollagen molecules are then transported through the Golgi apparatus into the extracellular space. The N- and C-terminal propeptides are cleaved by procollagen peptidases, converting procollagen into less soluble


Item 36 of 40
Question Id: 1245
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.
4. Procollagen molecules are then transported through the Golgi apparatus into the extracellular space. The N- and C-terminal propeptides are cleaved by procollagen peptidases, converting procollagen into less soluble tropocollagen.
5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:

Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen peptidase deficiency, which results in impaired cleavage of terminal propeptides in the extracellular space. Patients often have joint laxity, hyperextensible skin, and tissue fragility due to the formation of soluble collagen that does not properly crosslink.

References

- Defect in conversion of procollagen to collagen in a form of Ehlers-Danlos syndrome.
- Defects in the biochemistry of collagen in diseases of connective tissue.
- Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type.

Biochemistry
Subject

Biochemistry (General Principles)
System

Ehlers danlos syndrome
Topic

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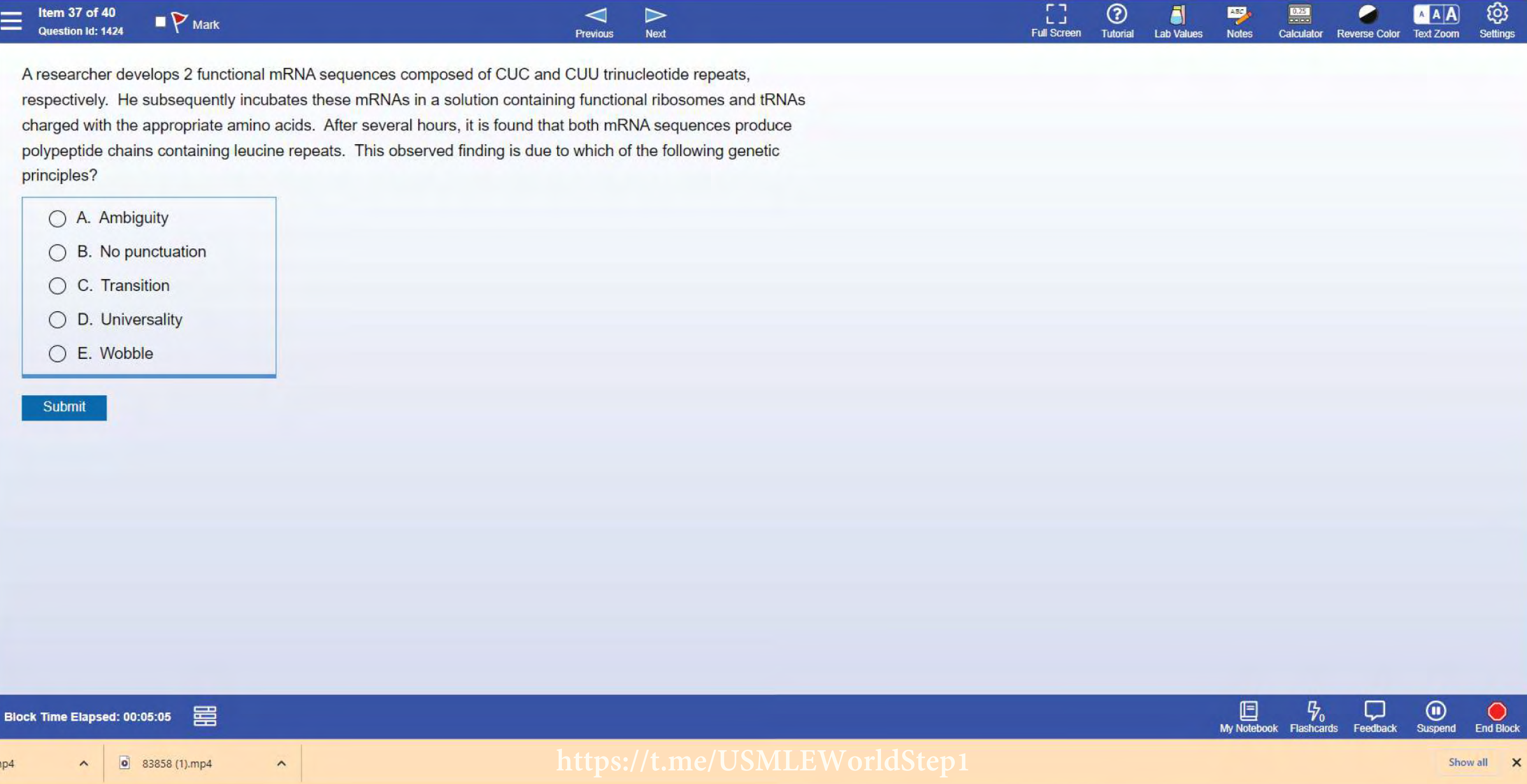
Item 37 of 40
Question Id: 1424
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

○ A. Ambiguity
○ B. No punctuation
○ C. Transition
○ D. Universality
○ E. Wobble

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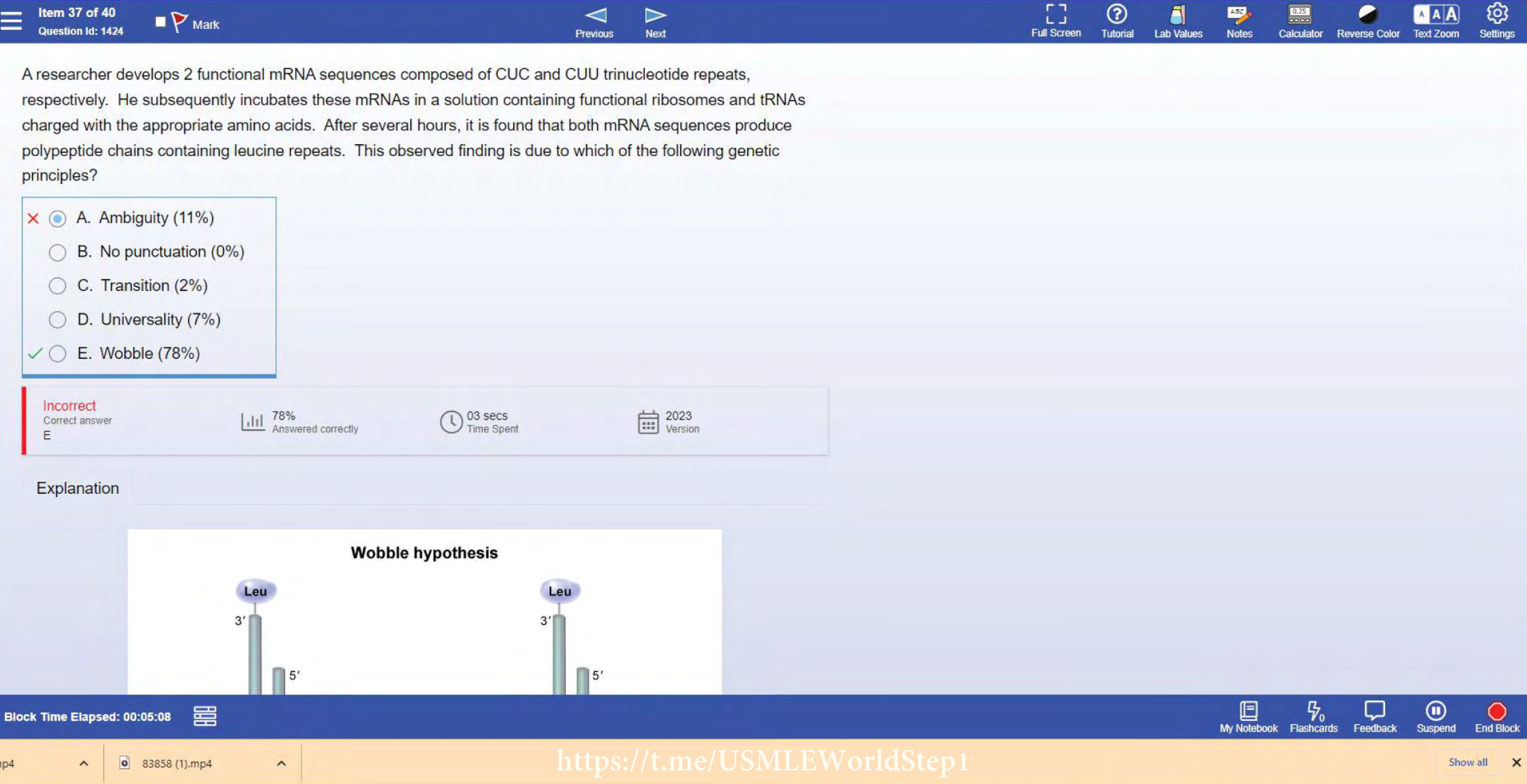
Item 37 of 40
Question Id: 1424
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✗ ● A. Ambiguity (11%)
- ○ B. No punctuation (0%)
- ○ C. Transition (2%)
- ○ D. Universality (7%)
- ✓ ○ E. Wobble (78%)

Incorrect
Correct answer
E

78%
Answered correctly

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Version

Explanation

Wobble hypothesis

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Block Time Elapsed: 00:05:08
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Feedback
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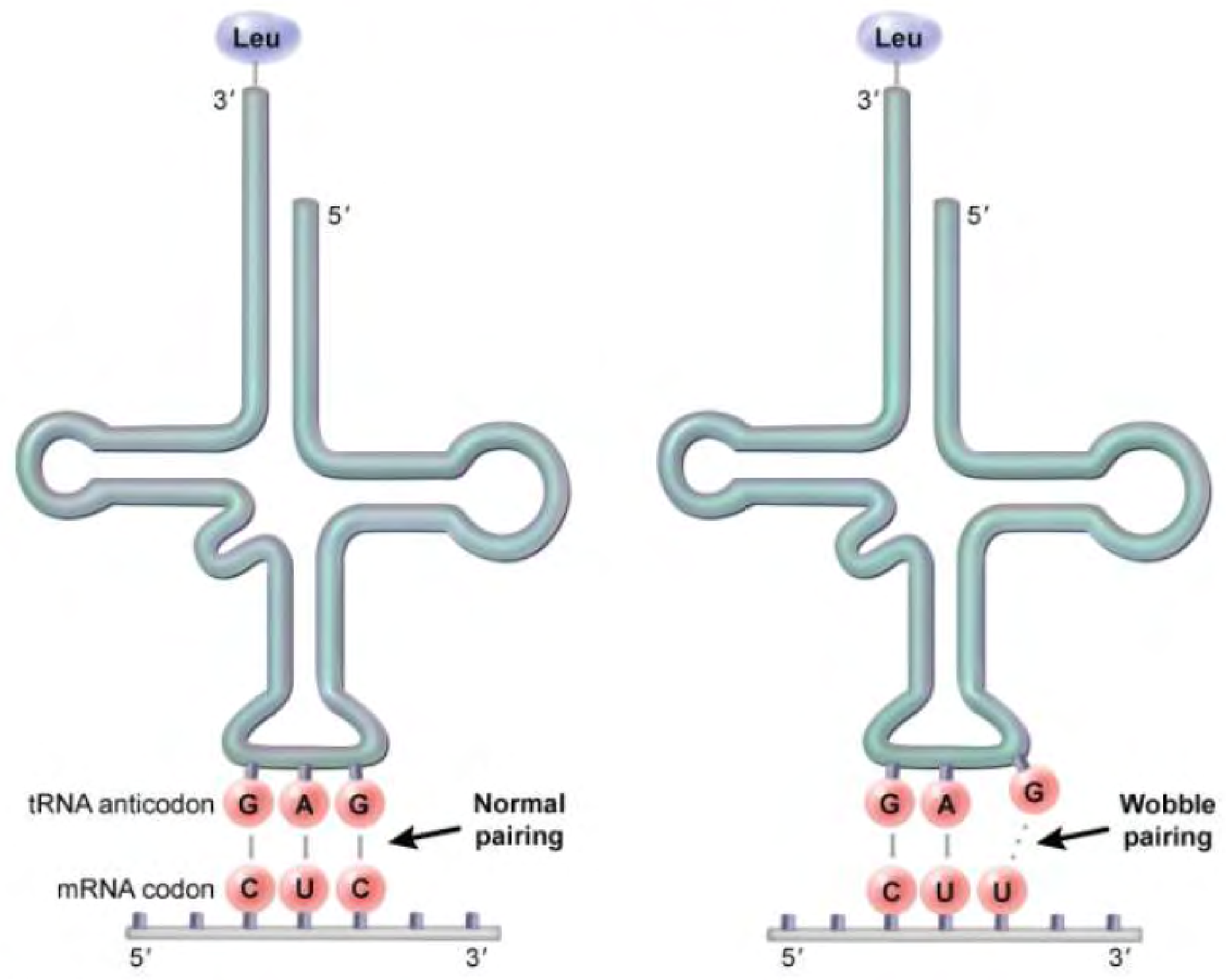
Wobble hypothesis

Exhibit Display

Wobble hypothesis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Wobble pairing
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those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino**

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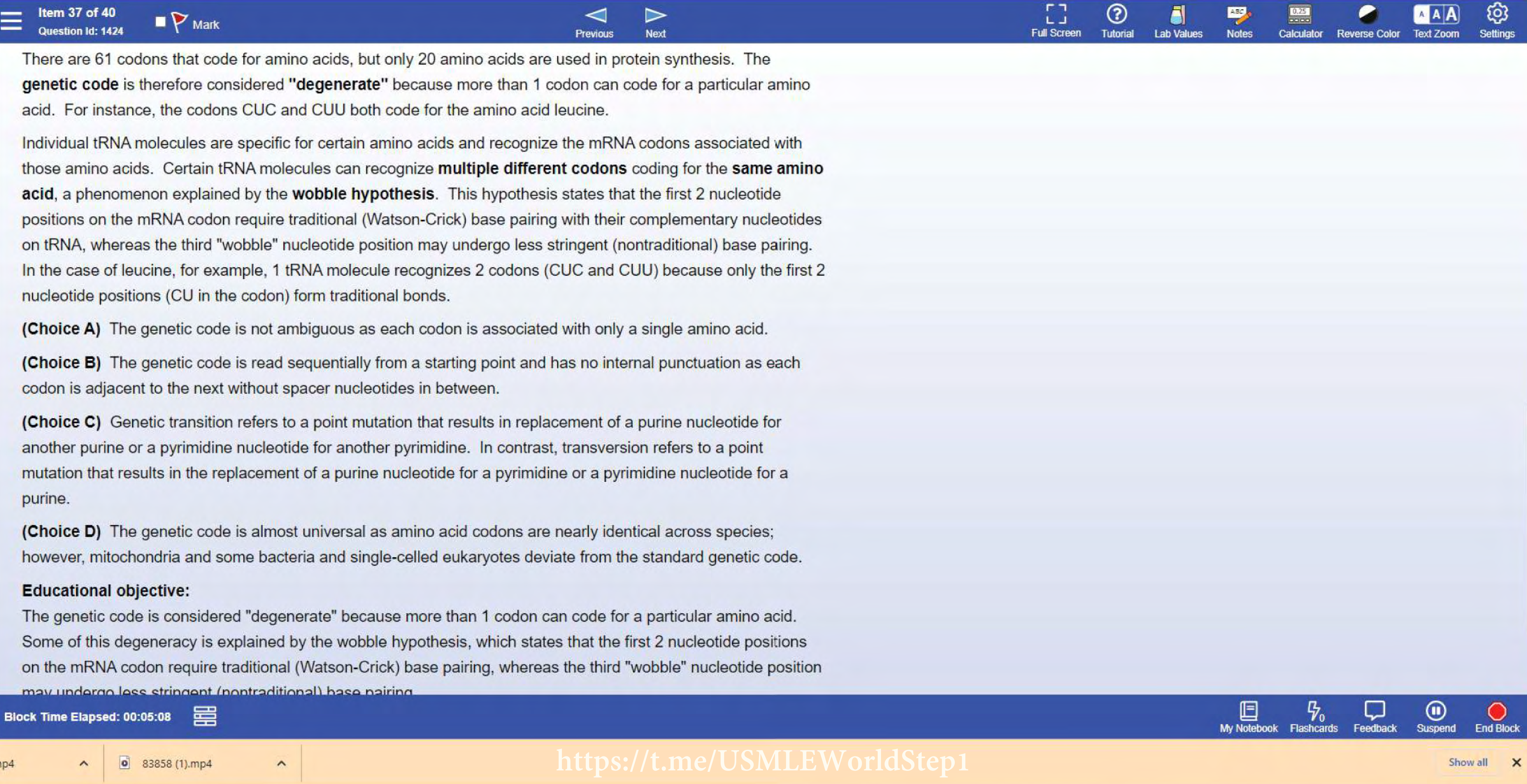


There are 61 codons that code for amino acids, but only 20 amino acids are used in protein synthesis. The **genetic code** is therefore considered **"degenerate"** because more than 1 codon can code for a particular amino acid. For instance, the codons CUC and CUU both code for the amino acid leucine.

Individual tRNA molecules are specific for certain amino acids and recognize the mRNA codons associated with those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino acid**, a phenomenon explained by the **wobble hypothesis**. This hypothesis states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing with their complementary nucleotides on tRNA, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing. In the case of leucine, for example, 1 tRNA molecule recognizes 2 codons (CUC and CUU) because only the first 2 nucleotide positions (CU in the codon) form traditional bonds.

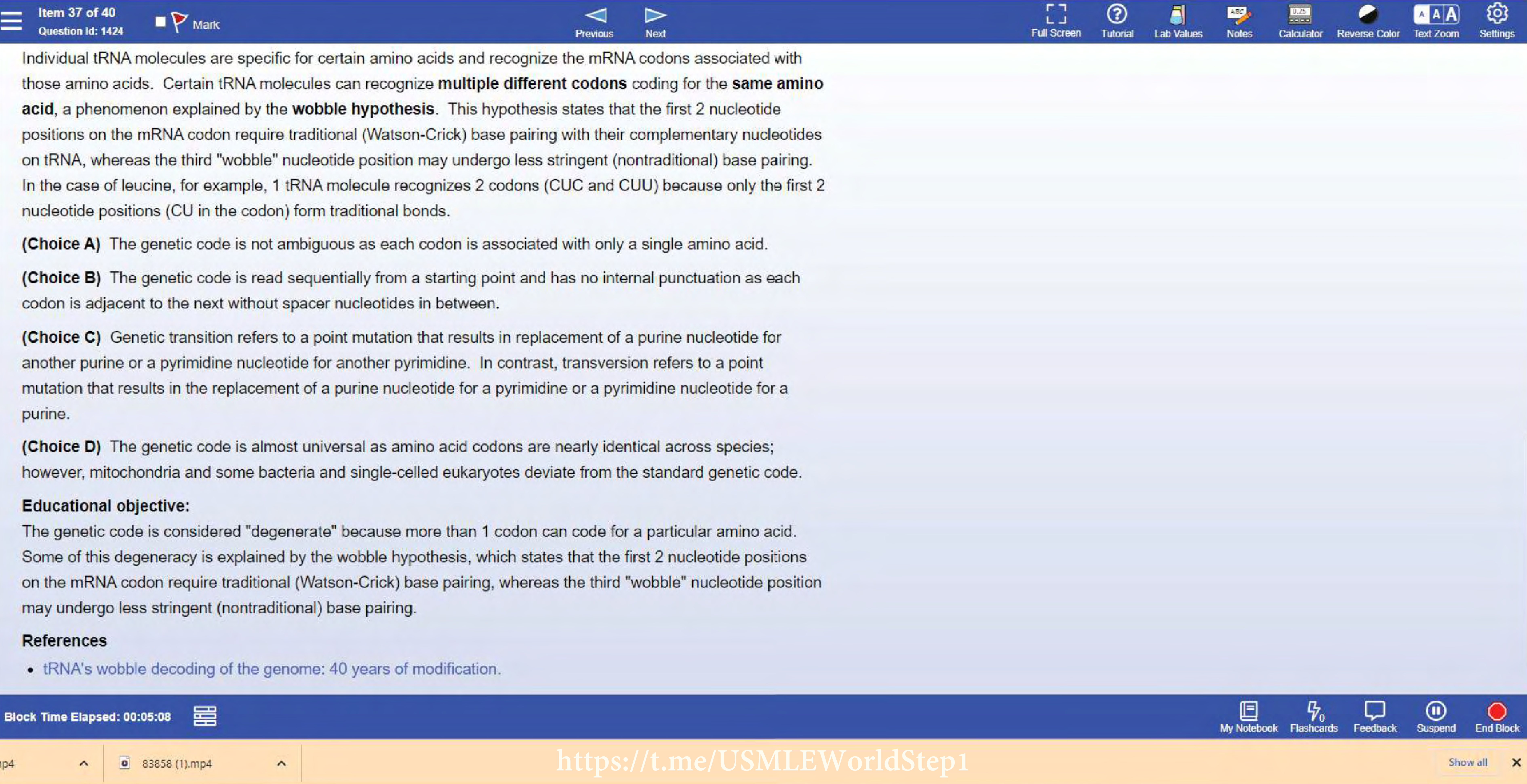
(Choice A) The genetic code is not ambiguous as each codon is associated with only a single amino acid.

(Choice B) The genetic code is read sequentially from a starting point and has no internal punctuation as each codon is adjacent to the next without spacer nucleotides in between.

(Choice C) Genetic transition refers to a point mutation that results in replacement of a purine nucleotide for another purine or a pyrimidine nucleotide for another pyrimidine. In contrast, transversion refers to a point mutation that results in the replacement of a purine nucleotide for a pyrimidine or a pyrimidine nucleotide for a purine.

(Choice D) The genetic code is almost universal as amino acid codons are nearly identical across species; however, mitochondria and some bacteria and single-celled eukaryotes deviate from the standard genetic code.

Educational objective:
The genetic code is considered "degenerate" because more than 1 codon can code for a particular amino acid. Some of this degeneracy is explained by the wobble hypothesis, which states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing.



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References

- tRNA's wobble decoding of the genome: 40 years of modification.

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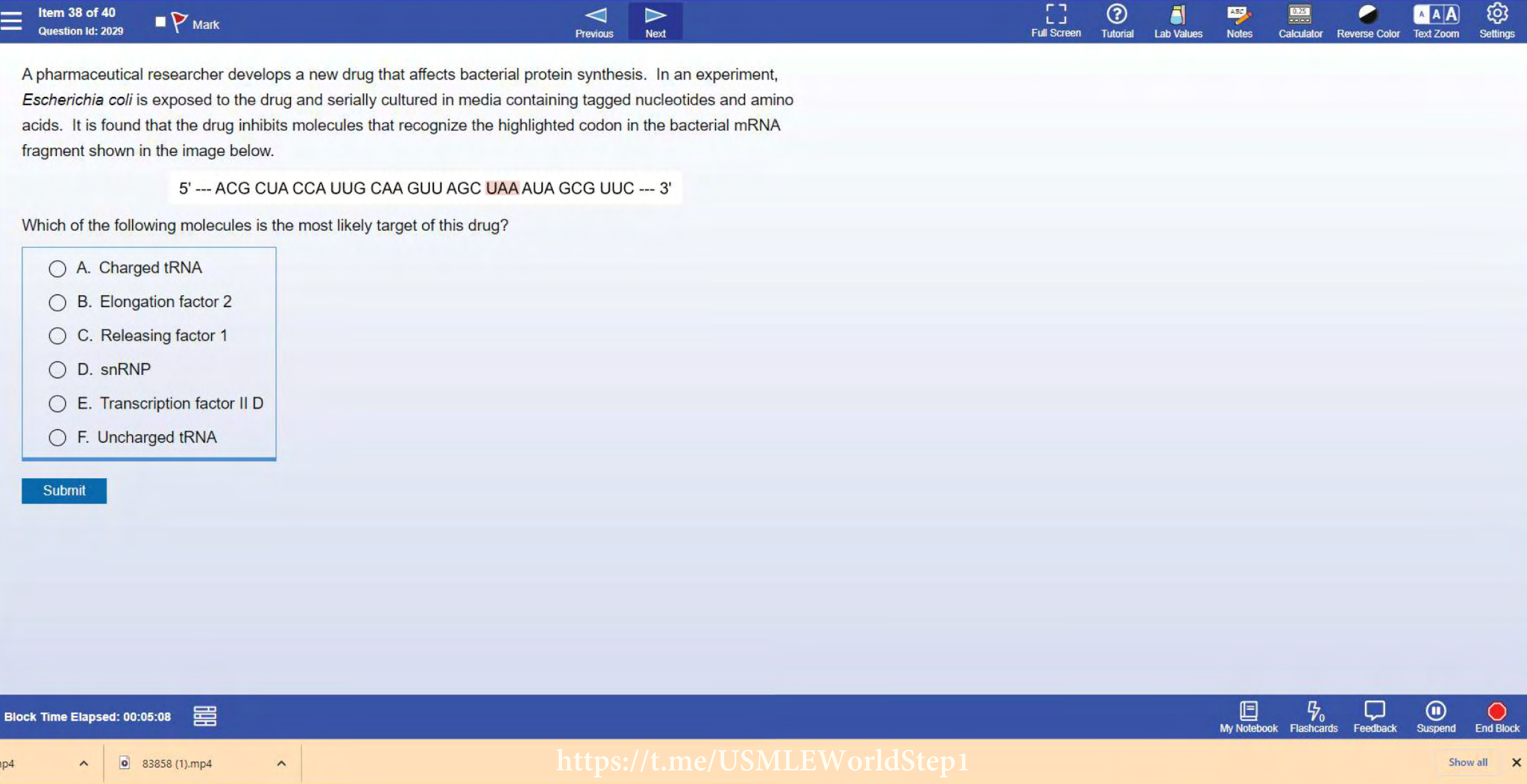
Item 38 of 40
Question Id: 2029
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical researcher develops a new drug that affects bacterial protein synthesis. In an experiment, *Escherichia coli* is exposed to the drug and serially cultured in media containing tagged nucleotides and amino acids. It is found that the drug inhibits molecules that recognize the highlighted codon in the bacterial mRNA fragment shown in the image below.

5' --- ACG CUA CCA UUG CAA GUU AGC UAA AUA GCG UUC --- 3'

Which of the following molecules is the most likely target of this drug?

- ○ A. Charged tRNA
- ○ B. Elongation factor 2
- ○ C. Releasing factor 1
- ○ D. snRNP
- ○ E. Transcription factor II D
- ○ F. Uncharged tRNA

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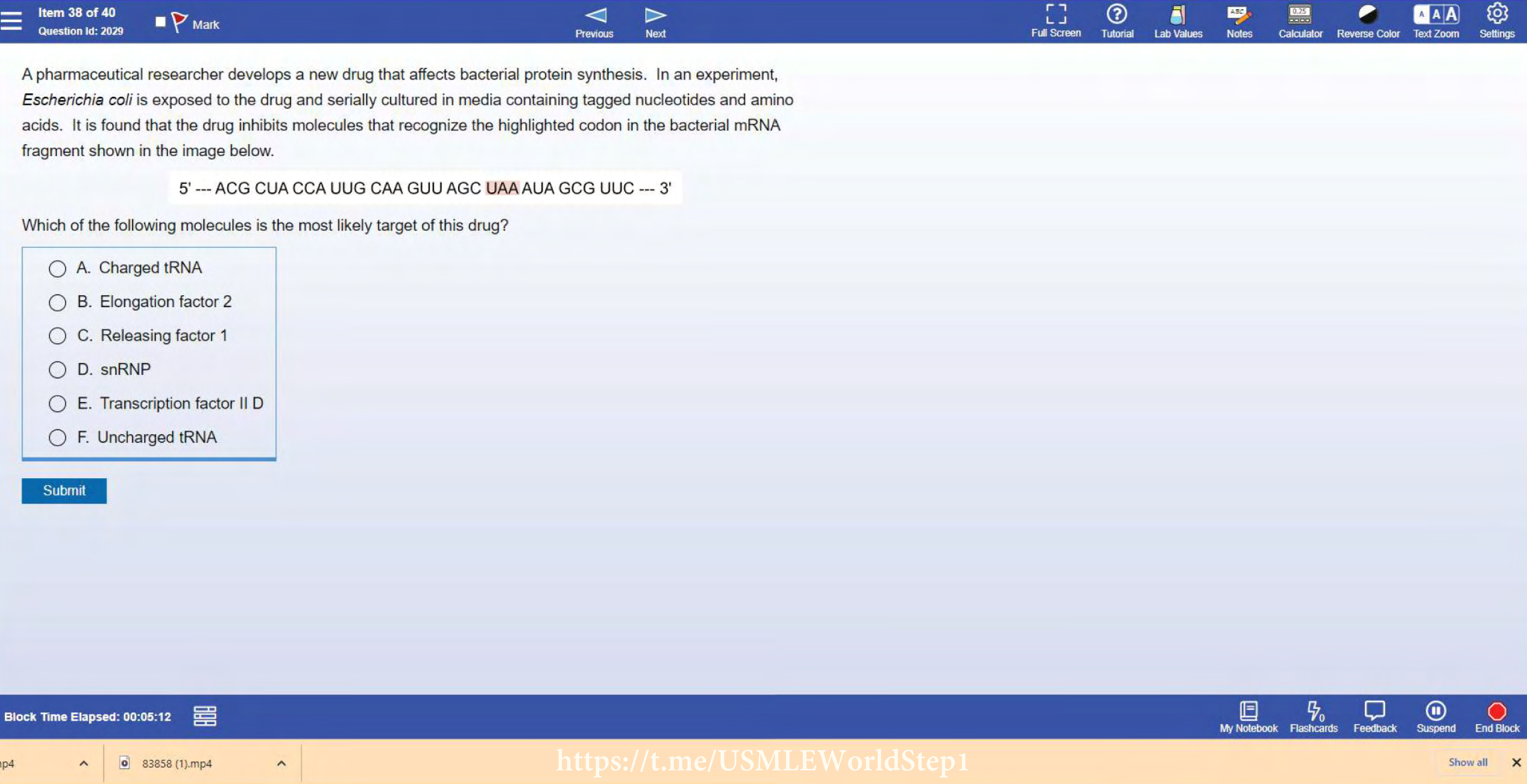
Item 38 of 40
Question Id: 2029
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ D. snRNP
○ E. Transcription factor II D
○ F. Uncharged tRNA

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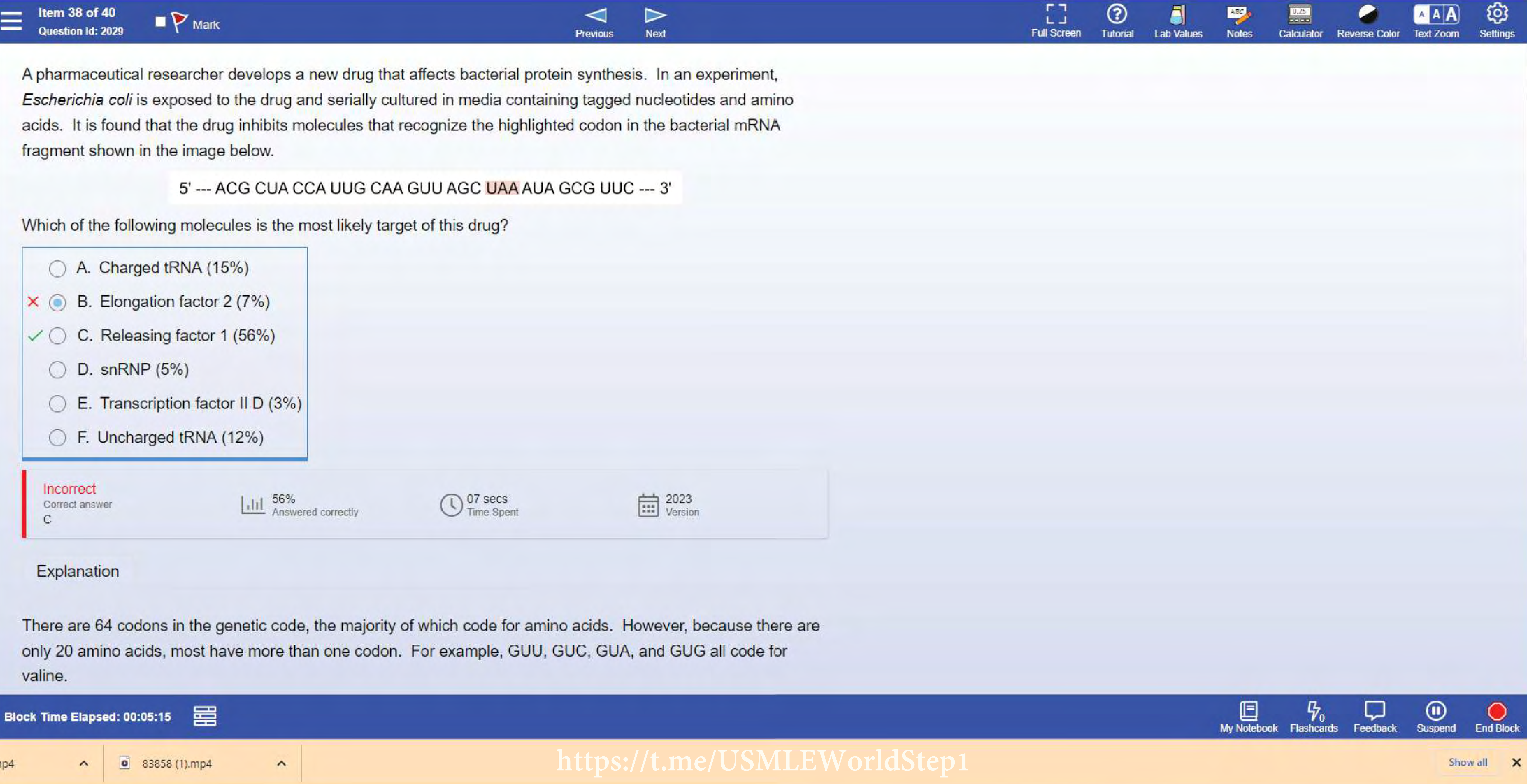
Item 38 of 40
Question Id: 2029
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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5' --- ACG CUA CCA UUG CAA GUU AGC UAA AUA GCG UUC --- 3'

Which of the following molecules is the most likely target of this drug?

○ A. Charged tRNA (15%)

✗ ● B. Elongation factor 2 (7%)

✓ ○ C. Releasing factor 1 (56%)

○ D. snRNP (5%)

○ E. Transcription factor II D (3%)

○ F. Uncharged tRNA (12%)

Incorrect
Correct answer
C

56%
Answered correctly

07 secs
Time Spent

2023
Version

Explanation

There are 64 codons in the genetic code, the majority of which code for amino acids. However, because there are only 20 amino acids, most have more than one codon. For example, GUU, GUC, GUA, and GUG all code for valine.

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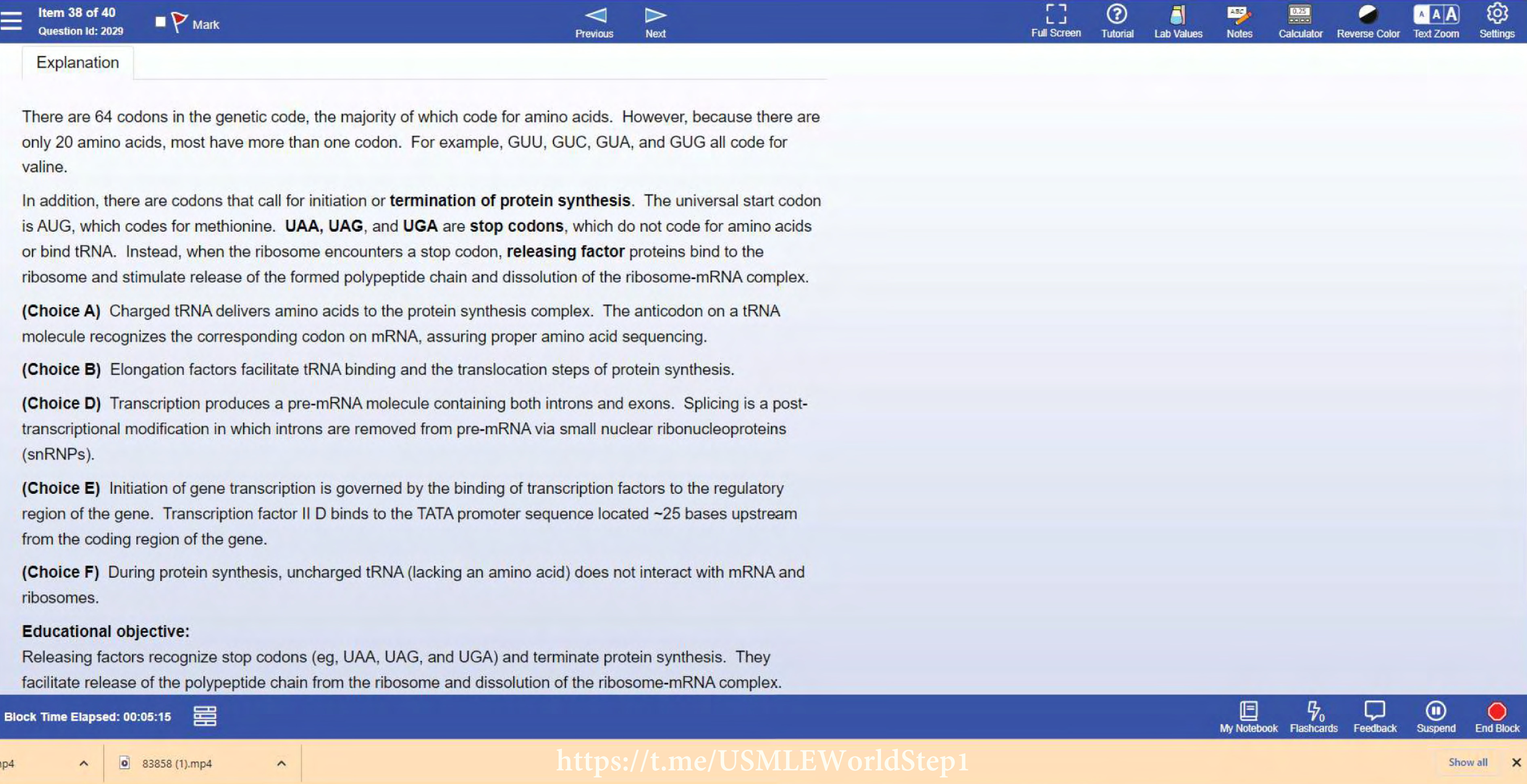
Item 38 of 40
Question Id: 2029
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Explanation

There are 64 codons in the genetic code, the majority of which code for amino acids. However, because there are only 20 amino acids, most have more than one codon. For example, GUU, GUC, GUA, and GUG all code for valine.

In addition, there are codons that call for initiation or **termination of protein synthesis**. The universal start codon is AUG, which codes for methionine. **UAA, UAG**, and **UGA** are **stop codons**, which do not code for amino acids or bind tRNA. Instead, when the ribosome encounters a stop codon, **releasing factor** proteins bind to the ribosome and stimulate release of the formed polypeptide chain and dissolution of the ribosome-mRNA complex.

(Choice A) Charged tRNA delivers amino acids to the protein synthesis complex. The anticodon on a tRNA molecule recognizes the corresponding codon on mRNA, assuring proper amino acid sequencing.

(Choice B) Elongation factors facilitate tRNA binding and the translocation steps of protein synthesis.

(Choice D) Transcription produces a pre-mRNA molecule containing both introns and exons. Splicing is a post-transcriptional modification in which introns are removed from pre-mRNA via small nuclear ribonucleoproteins (snRNPs).

(Choice E) Initiation of gene transcription is governed by the binding of transcription factors to the regulatory region of the gene. Transcription factor II D binds to the TATA promoter sequence located ~25 bases upstream from the coding region of the gene.

(Choice F) During protein synthesis, uncharged tRNA (lacking an amino acid) does not interact with mRNA and ribosomes.

Educational objective:

Releasing factors recognize stop codons (eg, UAA, UAG, and UGA) and terminate protein synthesis. They facilitate release of the polypeptide chain from the ribosome and dissolution of the ribosome-mRNA complex.

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Feedback
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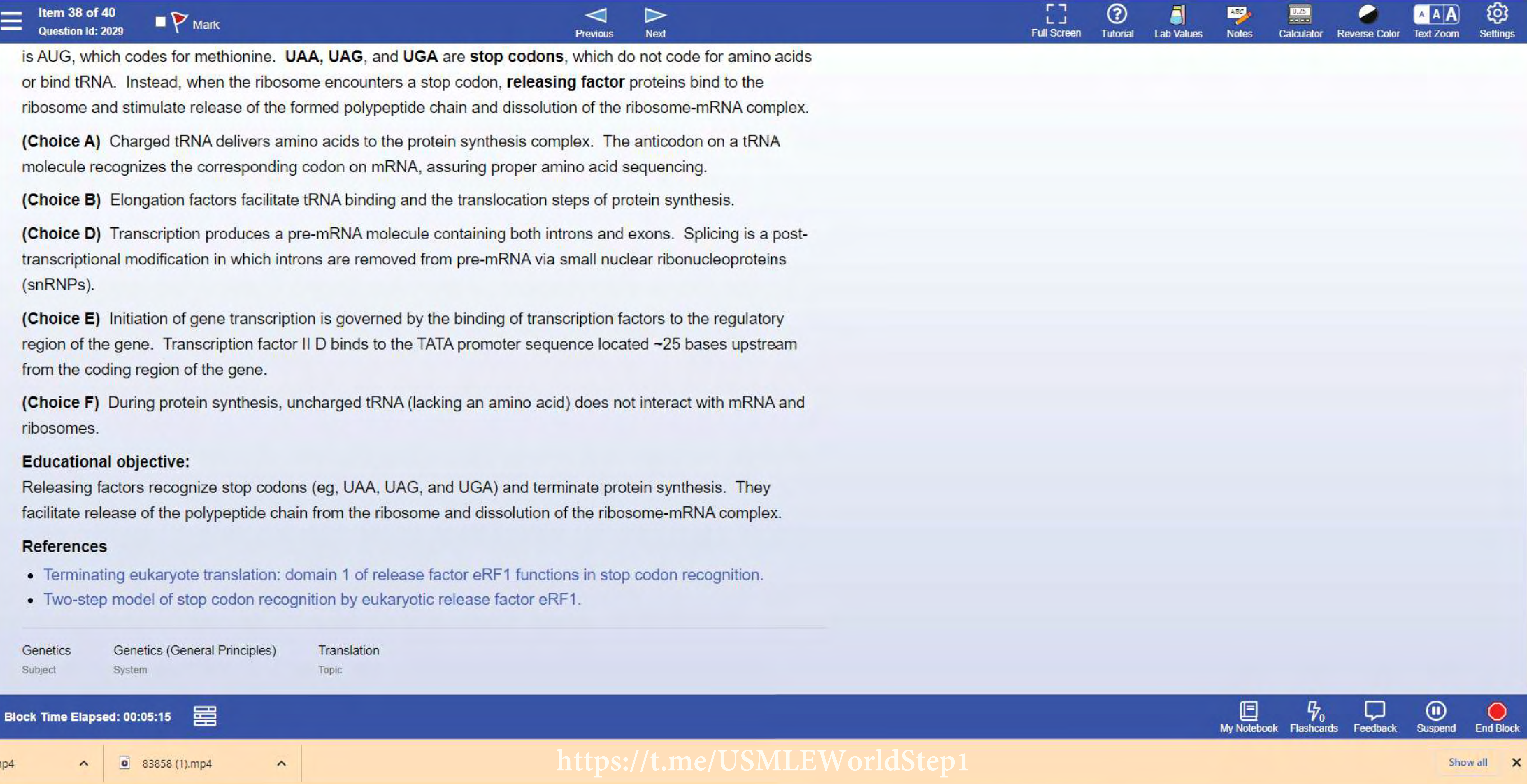
Item 38 of 40
Question Id: 2029
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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References

- Terminating eukaryote translation: domain 1 of release factor eRF1 functions in stop codon recognition.
- Two-step model of stop codon recognition by eukaryotic release factor eRF1.

Genetics	Genetics (General Principles)	Translation
Subject	System	Topic

Block Time Elapsed: 00:05:15
My Notebook
Flashcards
Feedback
Suspend
End Block
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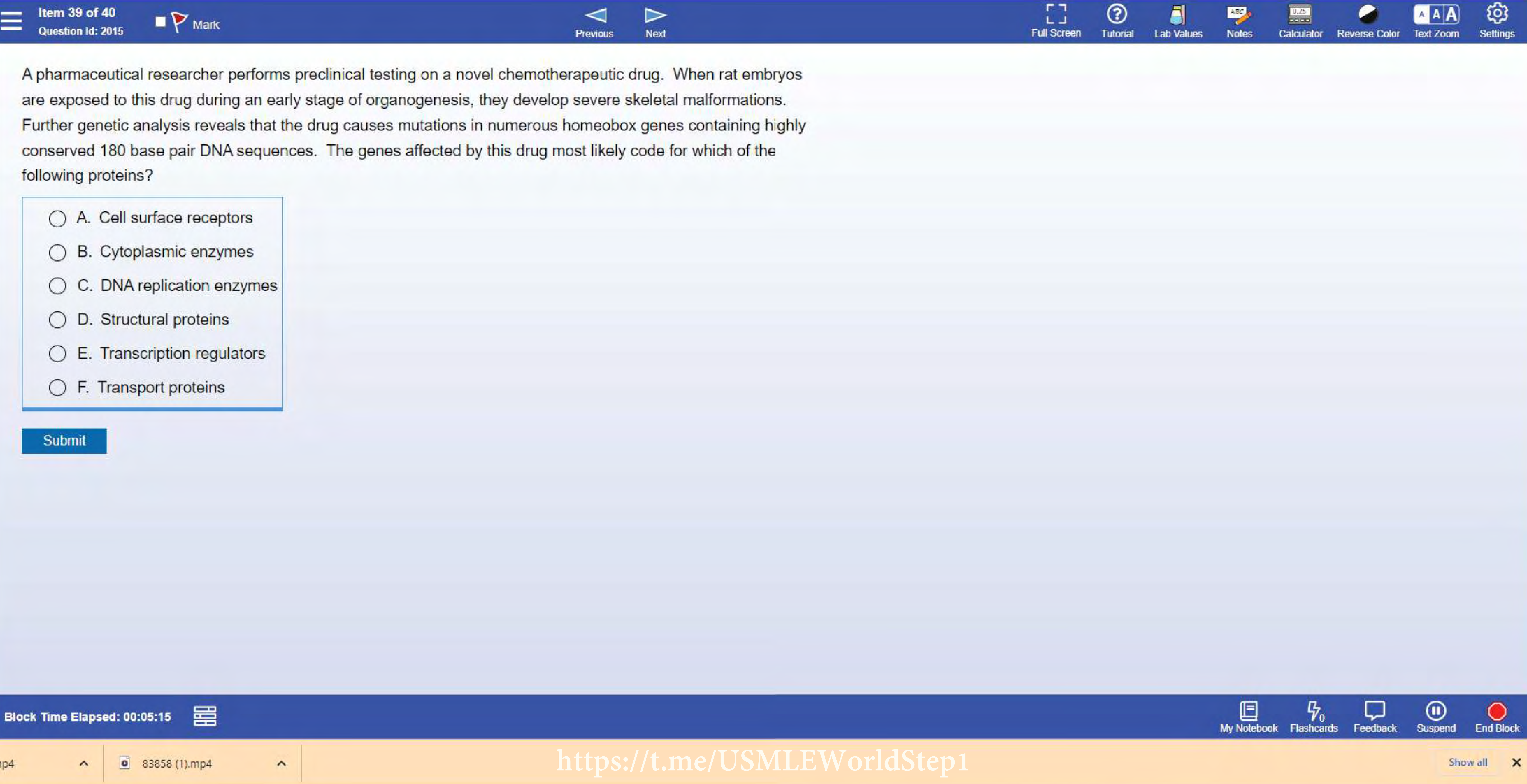
Item 39 of 40
Question Id: 2015
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical researcher performs preclinical testing on a novel chemotherapeutic drug. When rat embryos are exposed to this drug during an early stage of organogenesis, they develop severe skeletal malformations. Further genetic analysis reveals that the drug causes mutations in numerous homeobox genes containing highly conserved 180 base pair DNA sequences. The genes affected by this drug most likely code for which of the following proteins?

○ A. Cell surface receptors
○ B. Cytoplasmic enzymes
○ C. DNA replication enzymes
○ D. Structural proteins
○ E. Transcription regulators
○ F. Transport proteins

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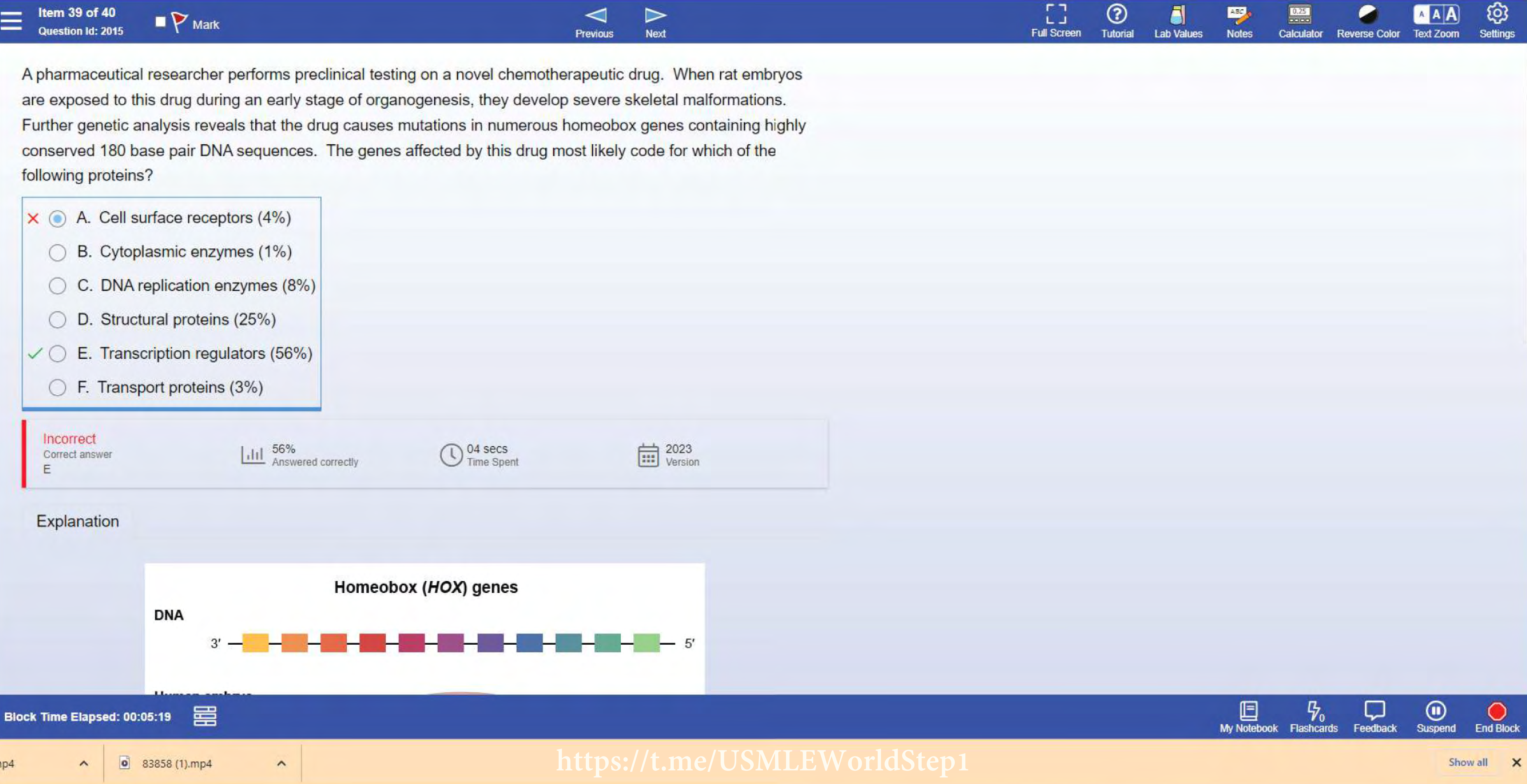
Item 39 of 40
Question Id: 2015
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✗ ● A. Cell surface receptors (4%)
- ○ B. Cytoplasmic enzymes (1%)
- ○ C. DNA replication enzymes (8%)
- ○ D. Structural proteins (25%)
- ✓ ○ E. Transcription regulators (56%)
- ○ F. Transport proteins (3%)

Incorrect
Correct answer
E

56%
Answered correctly

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2023
Version

Explanation

Homeobox (*HOX*) genes

Block Time Elapsed: 00:05:19
My Notebook
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Feedback
Suspend
End Block
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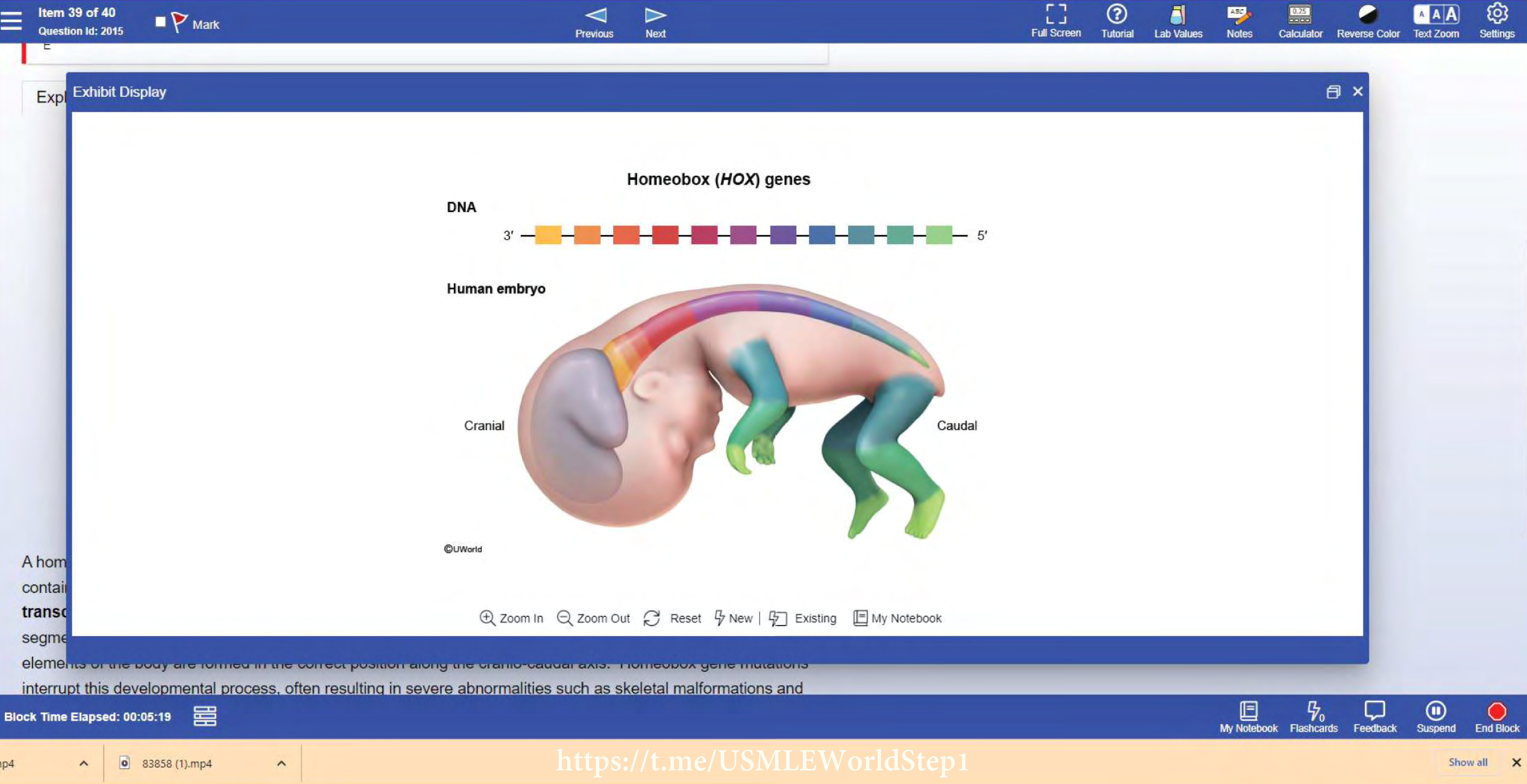

Item 39 of 40
Question Id: 2015
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
E
Expl
Exhibit Display

Homeobox (*HOX*) genes

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Caudal

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elements of the body are formed in the correct position along the cranio-caudal axis. Homeobox gene mutations interrupt this developmental process, often resulting in severe abnormalities such as skeletal malformations and

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Caudal
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A homeobox is a highly conserved DNA sequence that is usually about 180 nucleotides in length. A gene containing a homeobox sequence is called a **homeobox** or **hox gene**. These genes typically code for **transcription factors** that bind to regulatory regions on DNA, altering the expression of genes involved in the segmental organization of the embryo. Proper morphogenesis ensures that tissues, organs, and structural elements of the body are formed in the correct position along the cranio-caudal axis. Homeobox gene mutations interrupt this developmental process, often resulting in severe abnormalities such as skeletal malformations and improperly positioned limbs and appendages.

(Choices A, B, C, D, and F) Homeobox genes do not typically encode cell surface receptors, cytoplasmic enzymes, DNA replication enzymes, structural proteins, or transport proteins.

Educational objective:
Homeobox genes encode DNA-binding transcription factors that play an important role in the segmental organization of the embryo along the cranio-caudal axis.

References

- The regulation of Hox gene expression during animal development.

Genetics	Genetics (General Principles)	Transcription
Subject	System	Topic

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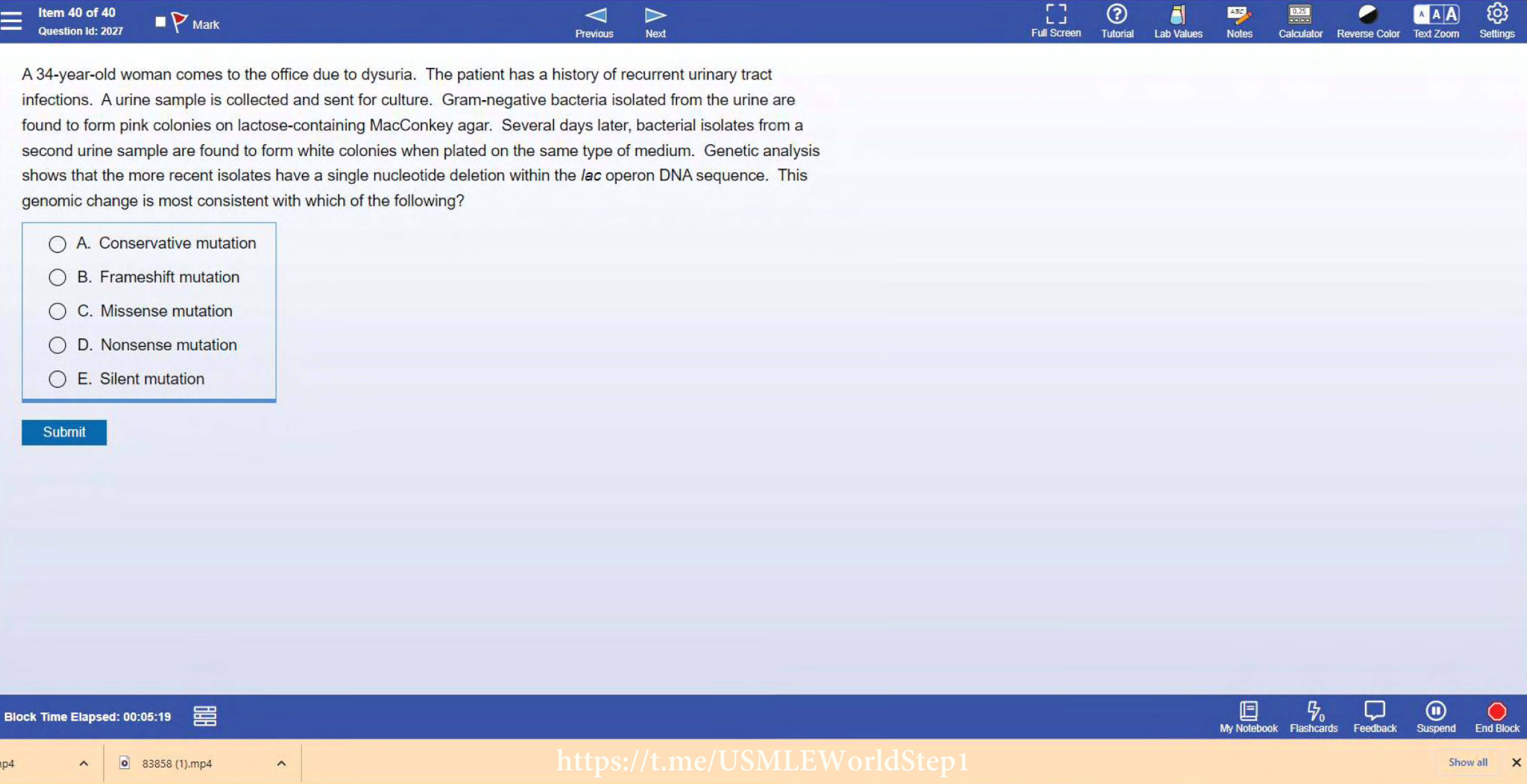
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 40 of 40
Question Id: 2027

A 34-year-old woman comes to the office due to dysuria. The patient has a history of recurrent urinary tract infections. A urine sample is collected and sent for culture. Gram-negative bacteria isolated from the urine are found to form pink colonies on lactose-containing MacConkey agar. Several days later, bacterial isolates from a second urine sample are found to form white colonies when plated on the same type of medium. Genetic analysis shows that the more recent isolates have a single nucleotide deletion within the *lac* operon DNA sequence. This genomic change is most consistent with which of the following?

○ A. Conservative mutation
○ B. Frameshift mutation
○ C. Missense mutation
○ D. Nonsense mutation
○ E. Silent mutation

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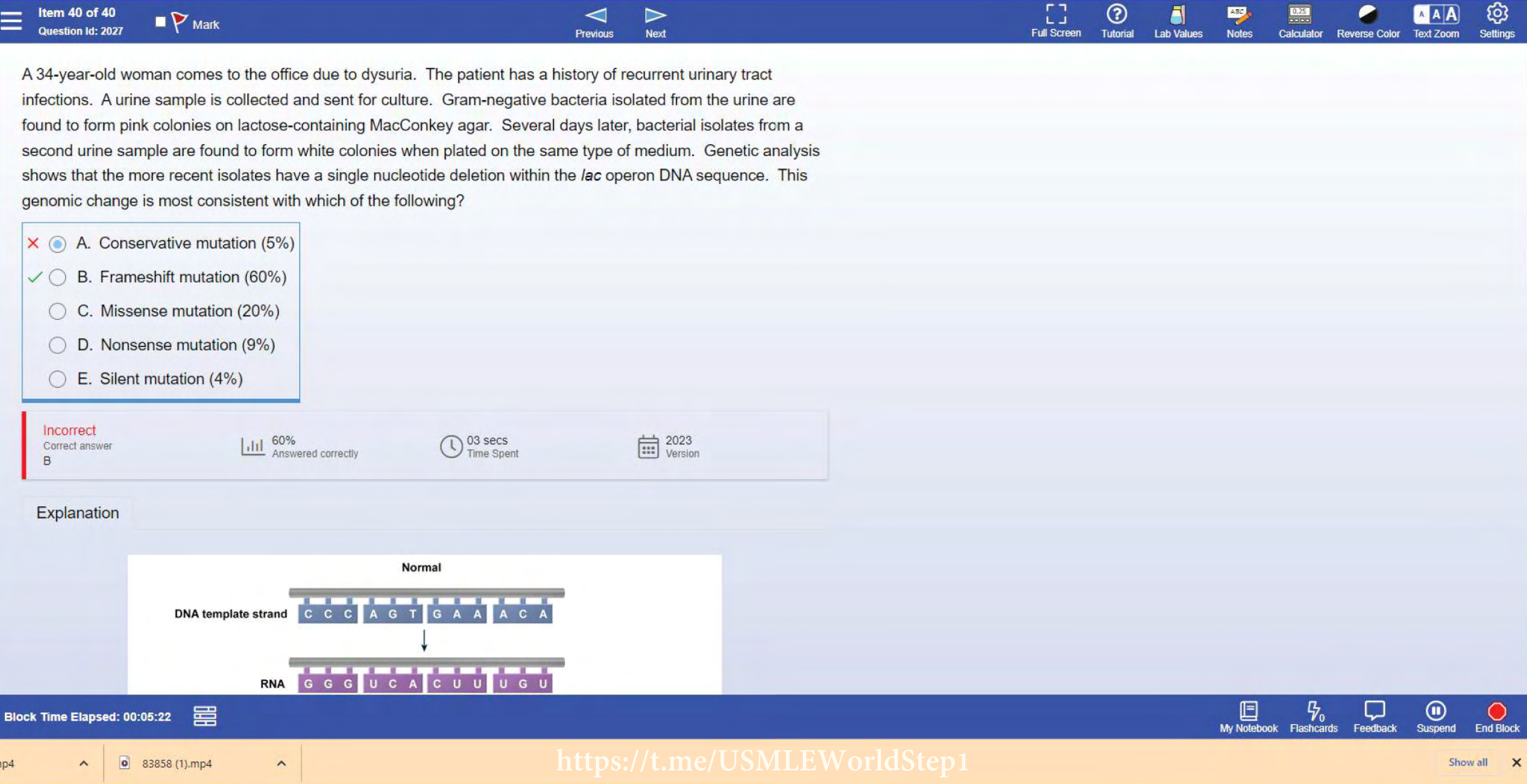

Item 40 of 40
Question Id: 2027
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ✗ ● A. Conservative mutation (5%)
- ✓ ○ B. Frameshift mutation (60%)
- ○ C. Missense mutation (20%)
- ○ D. Nonsense mutation (9%)
- ○ E. Silent mutation (4%)

Incorrect
Correct answer
B

60%
Answered correctly

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Explanation

Normal
DNA template strand
C C C A G T G A A A C A
RNA
G G G U C A C U U U G U

Block Time Elapsed: 00:05:22
My Notebook
Flashcards
Feedback
Suspend
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Show all

Item 40 of 40
Question Id: 2027

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

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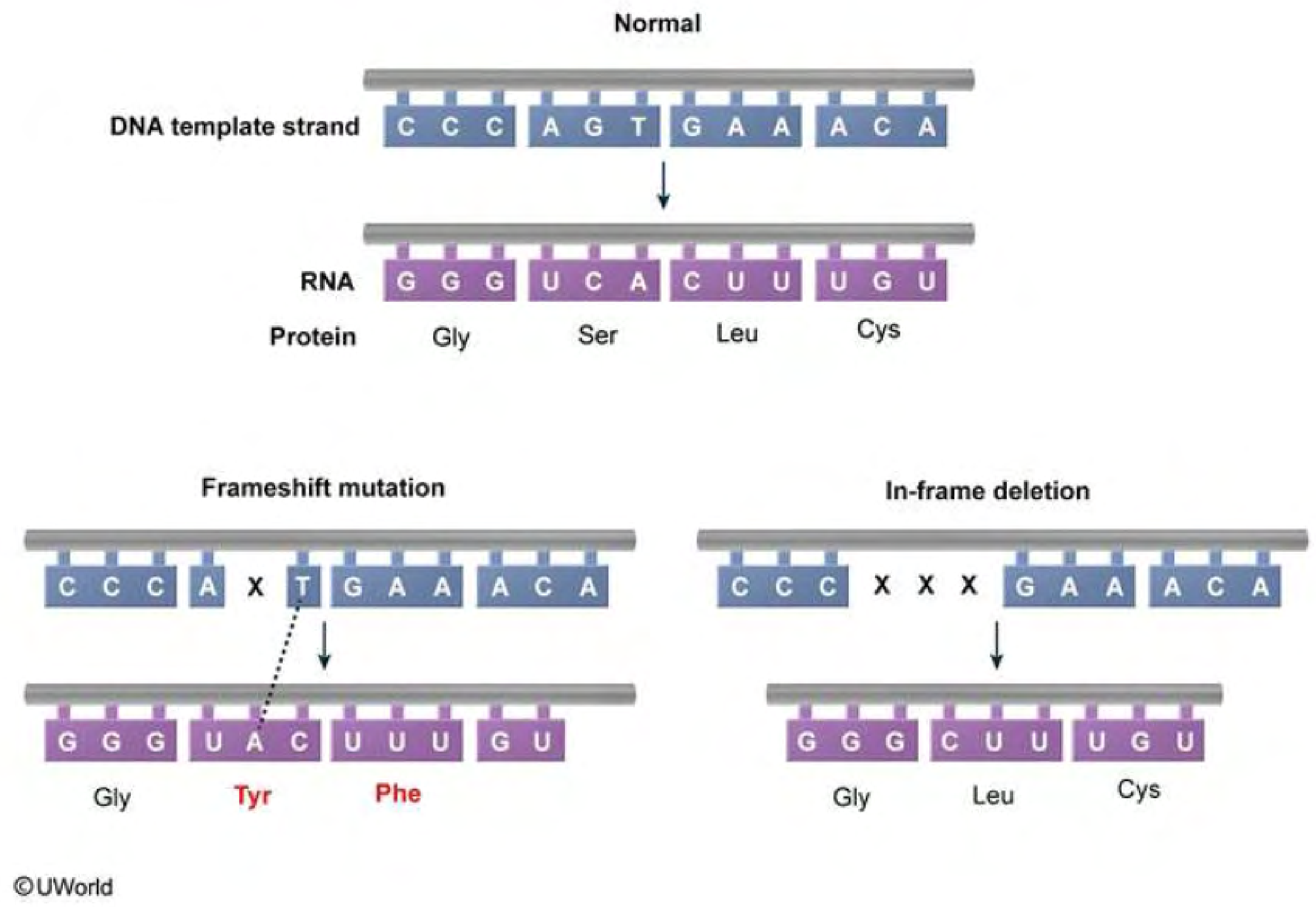
Normal
DNA template strand
C C C A G T G A A A C A
RNA
G G G U C A C U U U G U
Protein
Gly
Ser
Leu
Cys
Frameshift mutation
C C C A X T G A A A C A
G G G U A C U U U G U
Gly
Tyr
Phe
In-frame deletion
C C C X X X G A A A C A
G G G C U U U G U
Gly
Leu
Cys
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Organ

colonies. In this case, the single nucleotide deletion within the *lac* operon DNA sequence of the newer isolates

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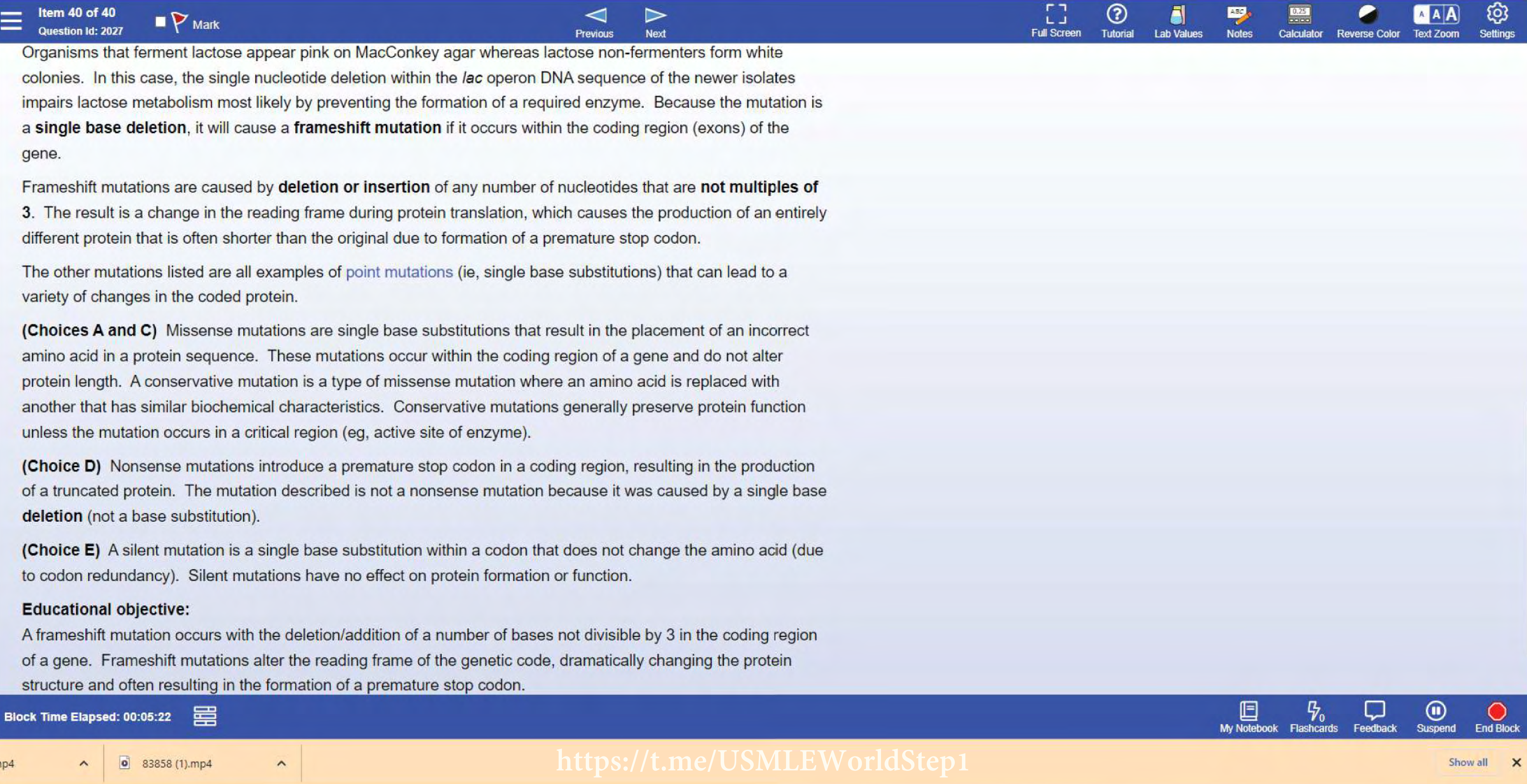


Organisms that ferment lactose appear pink on MacConkey agar whereas lactose non-fermenters form white colonies. In this case, the single nucleotide deletion within the *lac* operon DNA sequence of the newer isolates impairs lactose metabolism most likely by preventing the formation of a required enzyme. Because the mutation is a **single base deletion**, it will cause a **frameshift mutation** if it occurs within the coding region (exons) of the gene.

Frameshift mutations are caused by **deletion or insertion** of any number of nucleotides that are **not multiples of 3**. The result is a change in the reading frame during protein translation, which causes the production of an entirely different protein that is often shorter than the original due to formation of a premature stop codon.

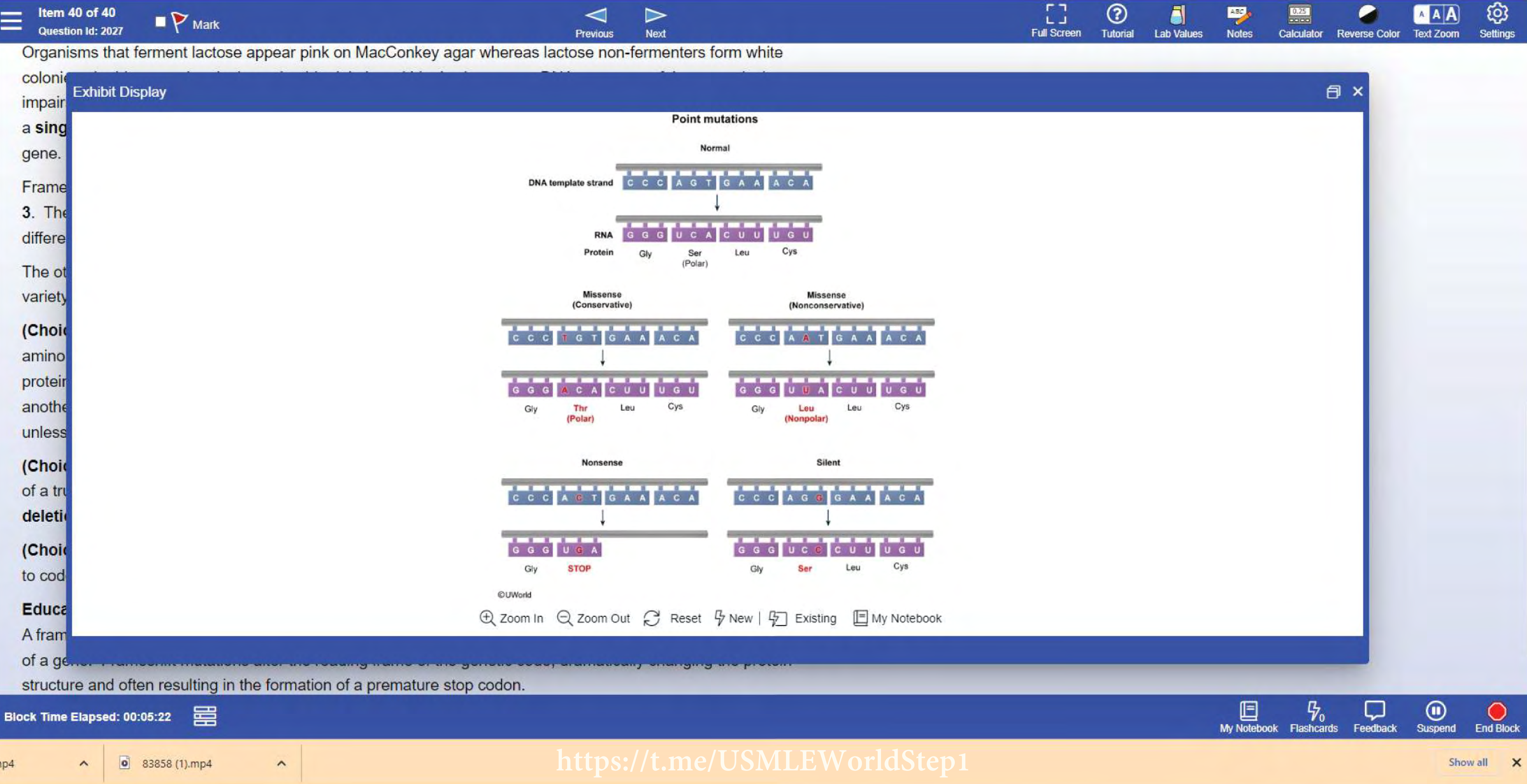
The other mutations listed are all examples of point mutations (ie, single base substitutions) that can lead to a variety of changes in the coded protein.

(Choices A and C) Missense mutations are single base substitutions that result in the placement of an incorrect amino acid in a protein sequence. These mutations occur within the coding region of a gene and do not alter protein length. A conservative mutation is a type of missense mutation where an amino acid is replaced with another that has similar biochemical characteristics. Conservative mutations generally preserve protein function unless the mutation occurs in a critical region (eg, active site of enzyme).

(Choice D) Nonsense mutations introduce a premature stop codon in a coding region, resulting in the production of a truncated protein. The mutation described is not a nonsense mutation because it was caused by a single base **deletion** (not a base substitution).

(Choice E) A silent mutation is a single base substitution within a codon that does not change the amino acid (due to codon redundancy). Silent mutations have no effect on protein formation or function.

Educational objective:
A frameshift mutation occurs with the deletion/addition of a number of bases not divisible by 3 in the coding region of a gene. Frameshift mutations alter the reading frame of the genetic code, dramatically changing the protein structure and often resulting in the formation of a premature stop codon.


Item 40 of 40
Question Id: 2027
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Point mutations
Normal
DNA template strand
C C C A G T G A A A C A
RNA
G G G U C A C U U U G U
Protein
Gly
Ser
(Polar)
Leu
Cys
Missense
(Conservative)
C C C T G T G A A A C A
G G G A C A C U U U G U
Gly
Thr
(Polar)
Leu
Cys
Missense
(Nonconservative)
C C C A A T G A A A C A
G G G U U A C U U U G U
Gly
Leu
(Nonpolar)
Leu
Cys
Nonsense
C C C A C T G A A A C A
G G G U G A
Gly
STOP
Silent
C C C A G G G A A A C A
G G G U C C C U U U G U
Gly
Ser
Leu
Cys
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Organisms that ferment lactose appear pink on MacConkey agar whereas lactose non-fermenters form white

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structure and often resulting in the formation of a premature stop codon.

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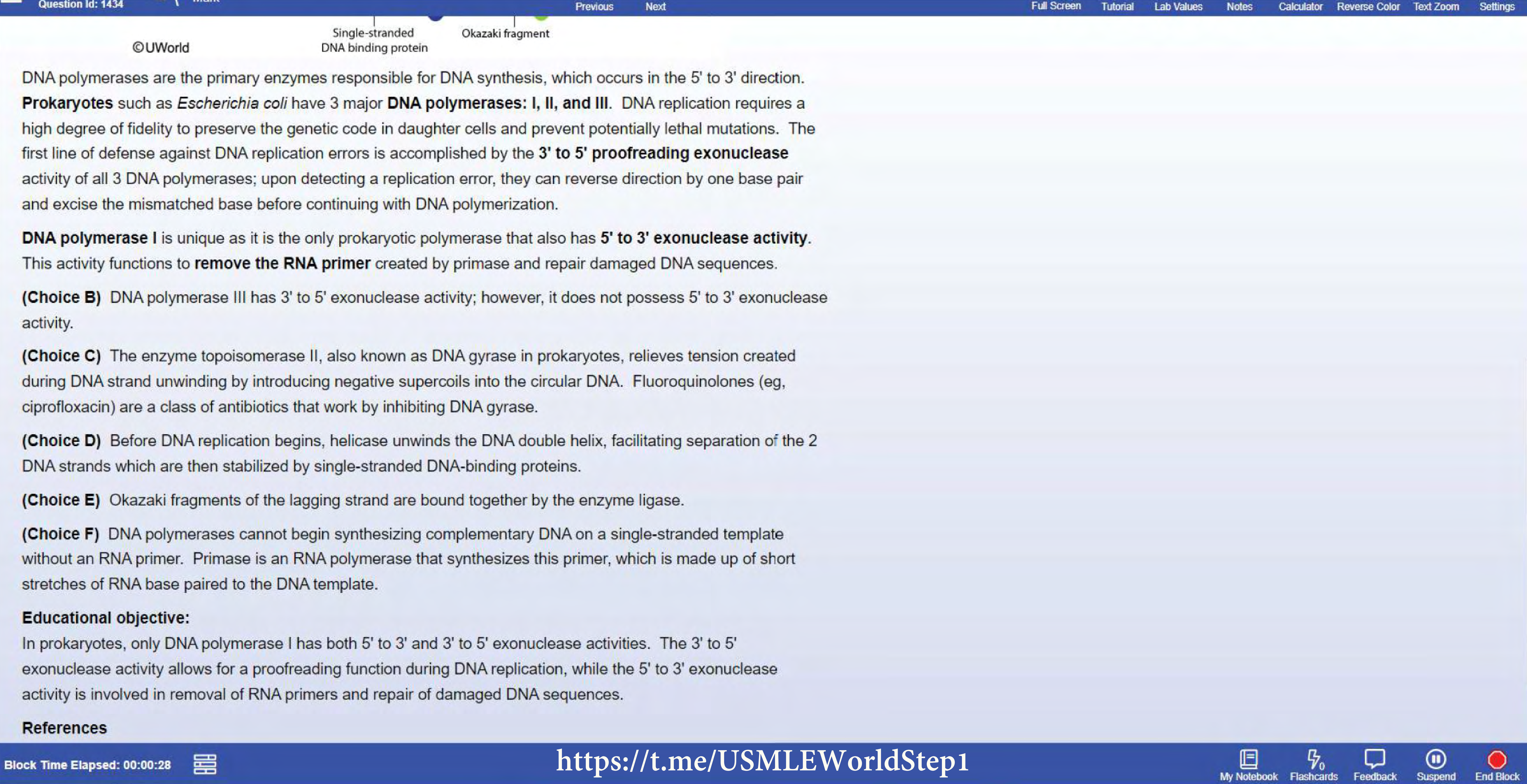
Question Id: 1434
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Single-stranded DNA binding protein
Okazaki fragment
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My Notebook
Flashcards
Feedback
Suspend
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DNA polymerases are the primary enzymes responsible for DNA synthesis, which occurs in the 5' to 3' direction. **Prokaryotes** such as *Escherichia coli* have 3 major **DNA polymerases: I, II, and III**. DNA replication requires a high degree of fidelity to preserve the genetic code in daughter cells and prevent potentially lethal mutations. The first line of defense against DNA replication errors is accomplished by the **3' to 5' proofreading exonuclease** activity of all 3 DNA polymerases; upon detecting a replication error, they can reverse direction by one base pair and excise the mismatched base before continuing with DNA polymerization.

DNA polymerase I is unique as it is the only prokaryotic polymerase that also has **5' to 3' exonuclease activity**. This activity functions to **remove the RNA primer** created by primase and repair damaged DNA sequences.

(Choice B) DNA polymerase III has 3' to 5' exonuclease activity; however, it does not possess 5' to 3' exonuclease activity.

(Choice C) The enzyme topoisomerase II, also known as DNA gyrase in prokaryotes, relieves tension created during DNA strand unwinding by introducing negative supercoils into the circular DNA. Fluoroquinolones (eg, ciprofloxacin) are a class of antibiotics that work by inhibiting DNA gyrase.

(Choice D) Before DNA replication begins, helicase unwinds the DNA double helix, facilitating separation of the 2 DNA strands which are then stabilized by single-stranded DNA-binding proteins.

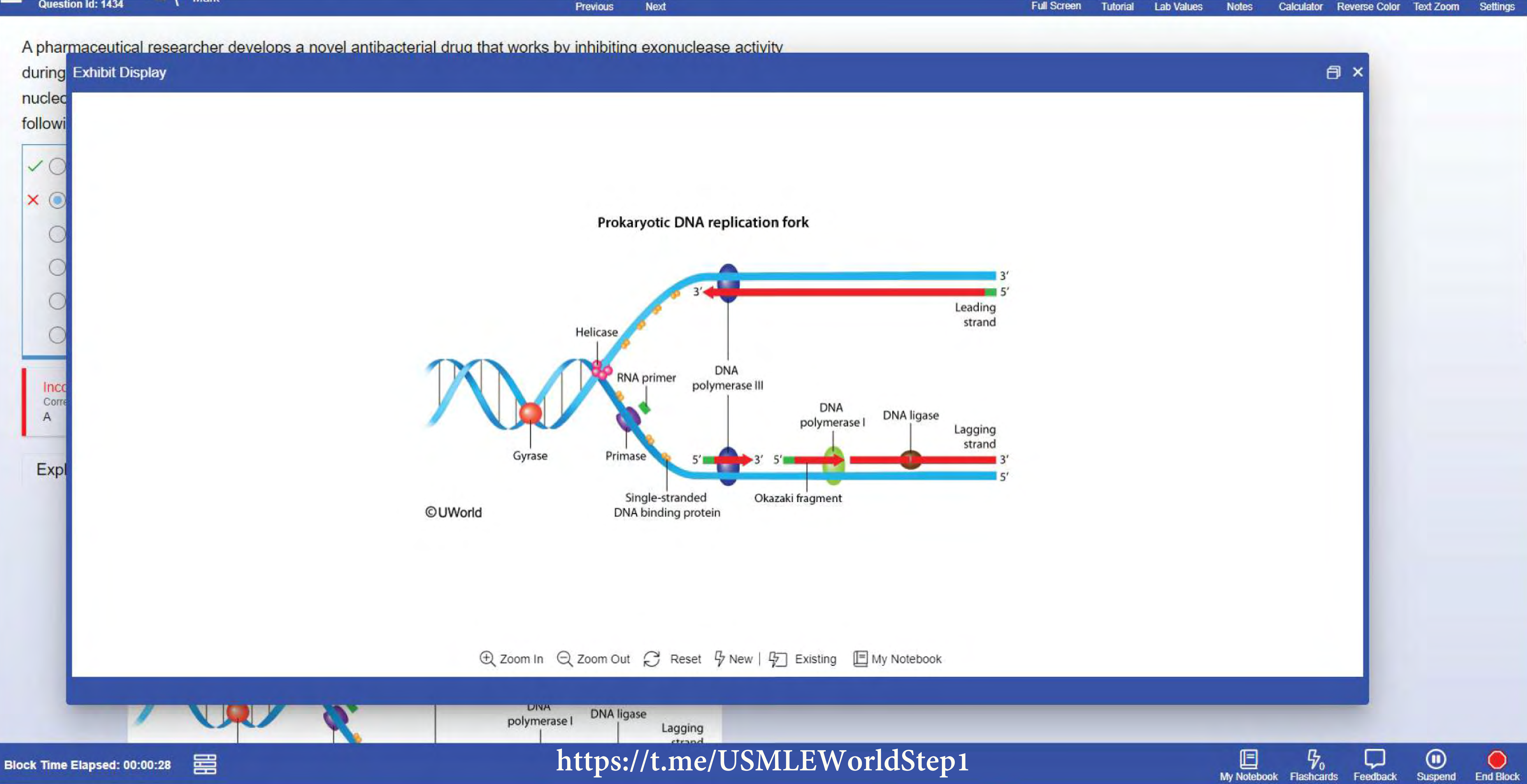
(Choice E) Okazaki fragments of the lagging strand are bound together by the enzyme ligase.

(Choice F) DNA polymerases cannot begin synthesizing complementary DNA on a single-stranded template without an RNA primer. Primase is an RNA polymerase that synthesizes this primer, which is made up of short stretches of RNA base paired to the DNA template.

Educational objective:

In prokaryotes, only DNA polymerase I has both 5' to 3' and 3' to 5' exonuclease activities. The 3' to 5' exonuclease activity allows for a proofreading function during DNA replication, while the 5' to 3' exonuclease activity is involved in removal of RNA primers and repair of damaged DNA sequences.

References



Question Id: 1434
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical researcher develops a novel antibacterial drug that works by inhibiting exonuclease activity

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Prokaryotic DNA replication fork

3′
5′
3′
Leading strand
Helicase
RNA primer
DNA polymerase III
DNA polymerase I
DNA ligase
Lagging strand
Gyrase
Primase
5′
3′
5′
3′
5′
Single-stranded DNA binding protein
Okazaki fragment

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Zoom In
Zoom Out
Reset
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My Notebook

Block Time Elapsed: 00:00:28

My Notebook
Flashcards
Feedback
Suspend
End Block

A pharmaceutical researcher develops a novel antibacterial drug that works by inhibiting exonuclease activity during DNA replication. When actively dividing *Escherichia coli* is exposed to the drug, enzyme-mediated nucleotide removal in the 5' to 3' direction is impaired, leading to inhibition of bacterial growth. Which of the following enzymes is the most likely target of this drug?

- ✓ ○ A. DNA polymerase I
- ✗ ● B. DNA polymerase III
- ○ C. Gyrase
- ○ D. Helicase
- ○ E. Ligase
- ○ F. Primase

Incorrect
Correct answer
A

Collecting Statistics

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2023
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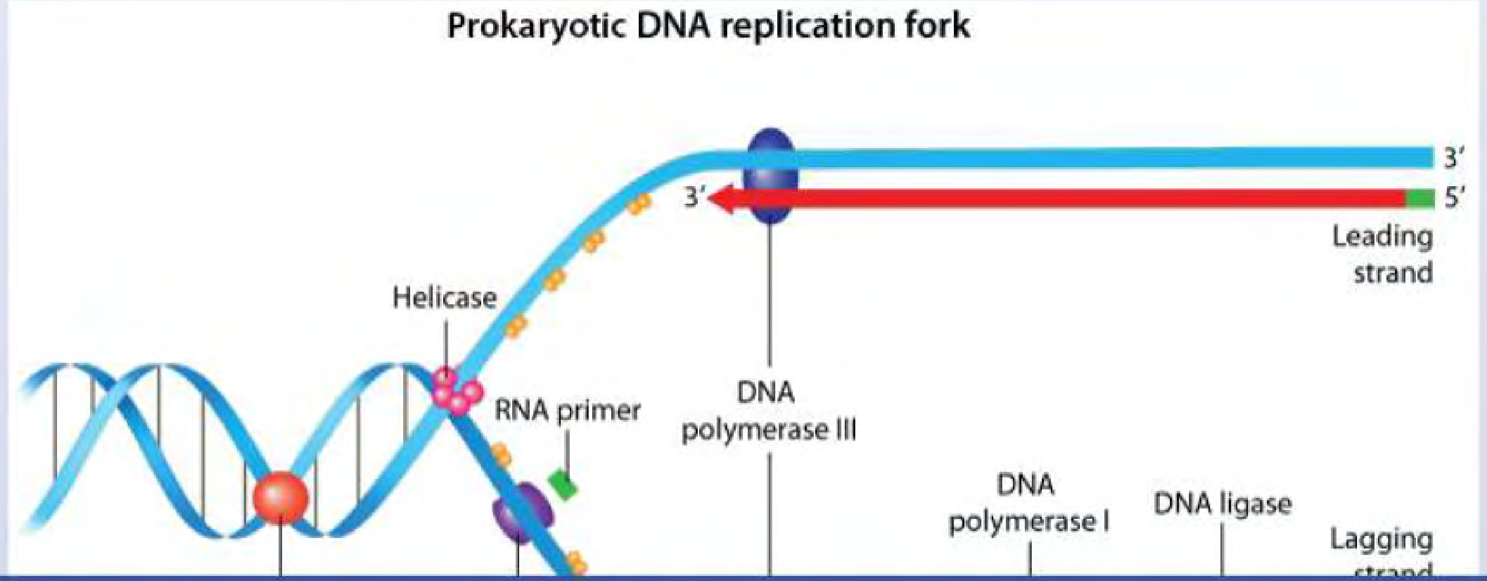
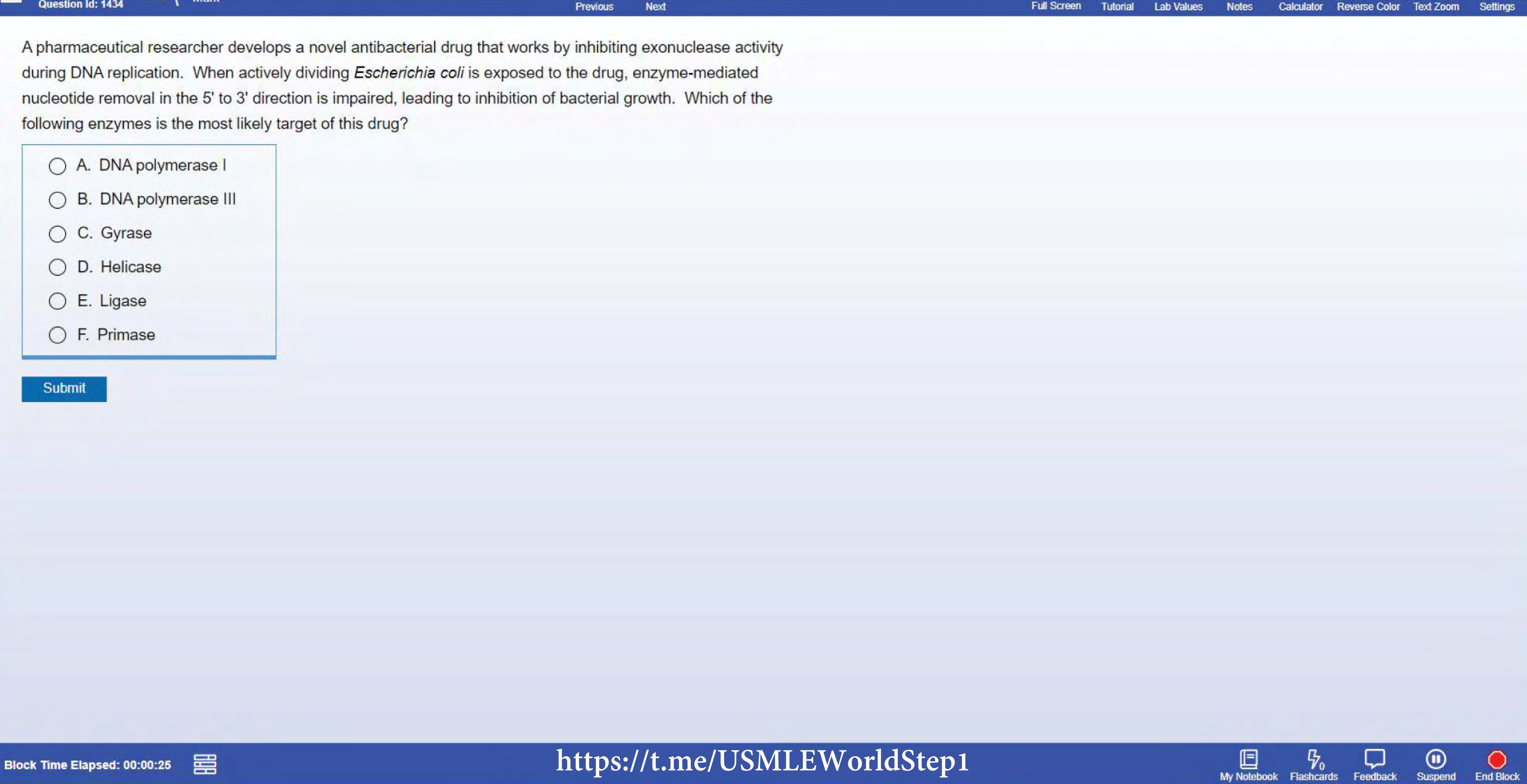
Explanation


Prokaryotic DNA replication fork
3'
5'
3'
Leading strand
Helicase
RNA primer
DNA polymerase III
DNA polymerase I
DNA ligase
Lagging strand


Question Id: 1434
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ B. DNA polymerase III

○ C. Gyrase

○ D. Helicase

○ E. Ligase

○ F. Primase

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Block Time Elapsed: 00:00:25
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 11 of 11
Question Id: 1418
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

synthesizes complementary daughter DNA strands.

Synthesis of the daughter strands occurs simultaneously from both parent strands. However, because **DNA synthesis can occur in only the 5′→3′ direction**, only 1 daughter strand is synthesized continuously toward the replication fork; this is the leading strand. The other strand, called the **lagging strand**, must be synthesized **discontinuously** in a direction away from the replication fork; more segments are added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are then removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase.

(Choice A) DNA polymerases have 3′→5′ exonuclease activity (proofreading function) that allows them to reverse direction and remove incorrectly placed bases. This process occurs on both newly formed daughter strands (not just the lagging strand) to help reduce replication errors.

(Choice B) DNA polymerases do not have 3′→5′ polymerase activity; all polymerases synthesize in the 5′→3′ direction.

(Choice C) During the synthesis of the lagging strand, 5′→3′ exonuclease activity is needed to remove RNA primers. However, it is also used to remove primers when joining leading strands from separate origins of replication and is therefore not a unique mechanism in the creation of the lagging strand.

(Choice D) Before DNA polymerase can initiate DNA synthesis, RNA primers must first be synthesized by the enzyme primase (DNA-dependent RNA polymerase). This process is necessary for synthesis of both daughter strands and is therefore not unique to the lagging strand.

Educational objective:

DNA synthesis occurs in the 5′→3′ direction only. During DNA replication, one daughter strand is synthesized continuously toward the replication fork (leading strand), whereas the other daughter strand is synthesized discontinuously away from the replication fork (lagging strand). The lagging strand is formed from short stretches of newly synthesized DNA separated by RNA primers (Okazaki fragments).

References

- Eukaryotic DNA replication fork

Block Time Elapsed: 00:00:58

Single-stranded DNA binding protein
Okazaki fragments
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DNA replication begins at **multiple sites**—origins of replication—within eukaryotic chromosomes. At these sites, the parent DNA double helix is separated and unwound in a process facilitated by the helicase enzyme and single-stranded DNA binding proteins. The locations at which unwound DNA meets the double helix are known as replication forks. Replication forks travel bidirectionally away from the origin of replication as DNA polymerase synthesizes complementary daughter DNA strands.

Synthesis of the daughter strands occurs simultaneously from both parent strands. However, because **DNA synthesis can occur in only the 5′→3′ direction**, only 1 daughter strand is synthesized continuously toward the replication fork; this is the leading strand. The other strand, called the **lagging strand**, must be synthesized **discontinuously** in a direction away from the replication fork; more segments are added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are then removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase.

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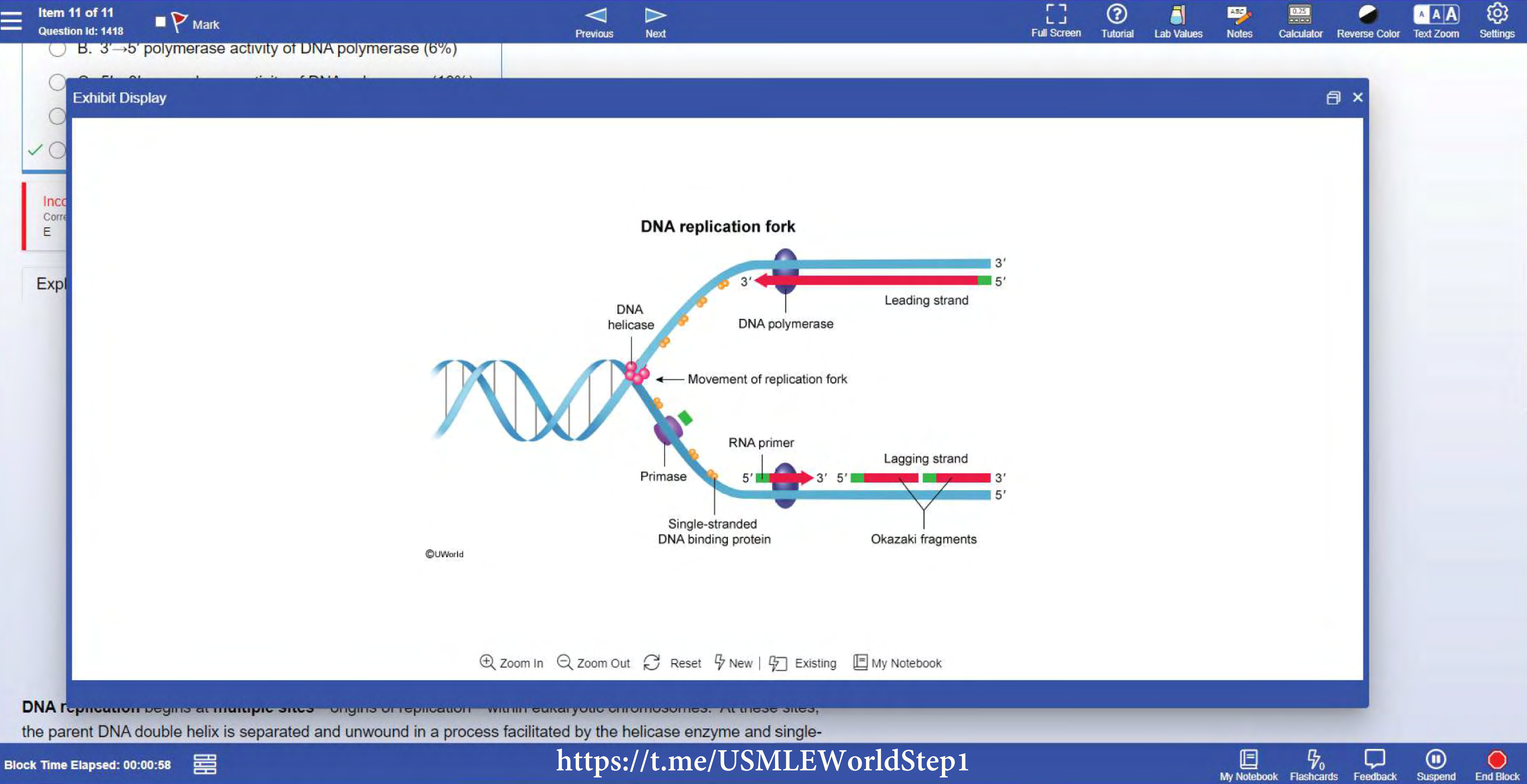
Item 11 of 11
Question Id: 1418
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:00:58
My Notebook
Flashcards
Feedback
Suspend
End Block

○ B. 3'→5' polymerase activity of DNA polymerase (6%)

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Expl

DNA replication fork

3'
5'
3'
Leading strand
DNA polymerase
DNA helicase
Movement of replication fork
RNA primer
Lagging strand
Primase
5'
3'
5'
3'
5'
Single-stranded DNA binding protein
Okazaki fragments

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DNA replication begins at **multiple sites**—origins of replication—within eukaryotic chromosomes. At these sites, the parent DNA double helix is separated and unwound in a process facilitated by the helicase enzyme and single-

A 4-year-old boy is brought to the office for evaluation of fatigue and bone pain. Physical examination shows diffuse lymphadenopathy and purpura over his arms and legs. Laboratory analysis reveals anemia and thrombocytopenia, and a peripheral blood smear shows lymphoblasts. After further work-up, acute lymphoblastic leukemia is diagnosed, and the patient begins a chemotherapy regimen that includes doxorubicin. This agent intercalates between DNA base pairs and inhibits DNA replication, a process that normally occurs at replication forks and produces 2 distinct daughter strands. Which of the following is unique to the daughter strand that is synthesized in the opposite direction of the growing replication fork?

✗ ● A. 3′→5′ exonuclease activity of DNA polymerase (10%)
○ B. 3′→5′ polymerase activity of DNA polymerase (6%)
○ C. 5′→3′ exonuclease activity of DNA polymerase (10%)
○ D. RNA primer synthesis before DNA strand synthesis (7%)
✓ ○ E. Synthesis of multiple, short DNA fragments (64%)

Incorrect
Correct answer
E

64%
Answered correctly

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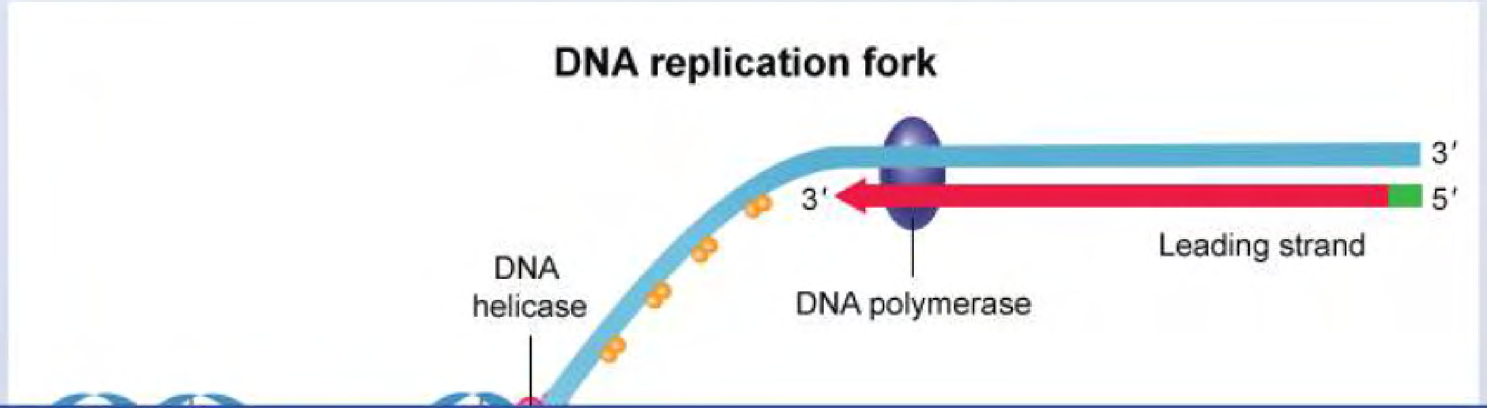
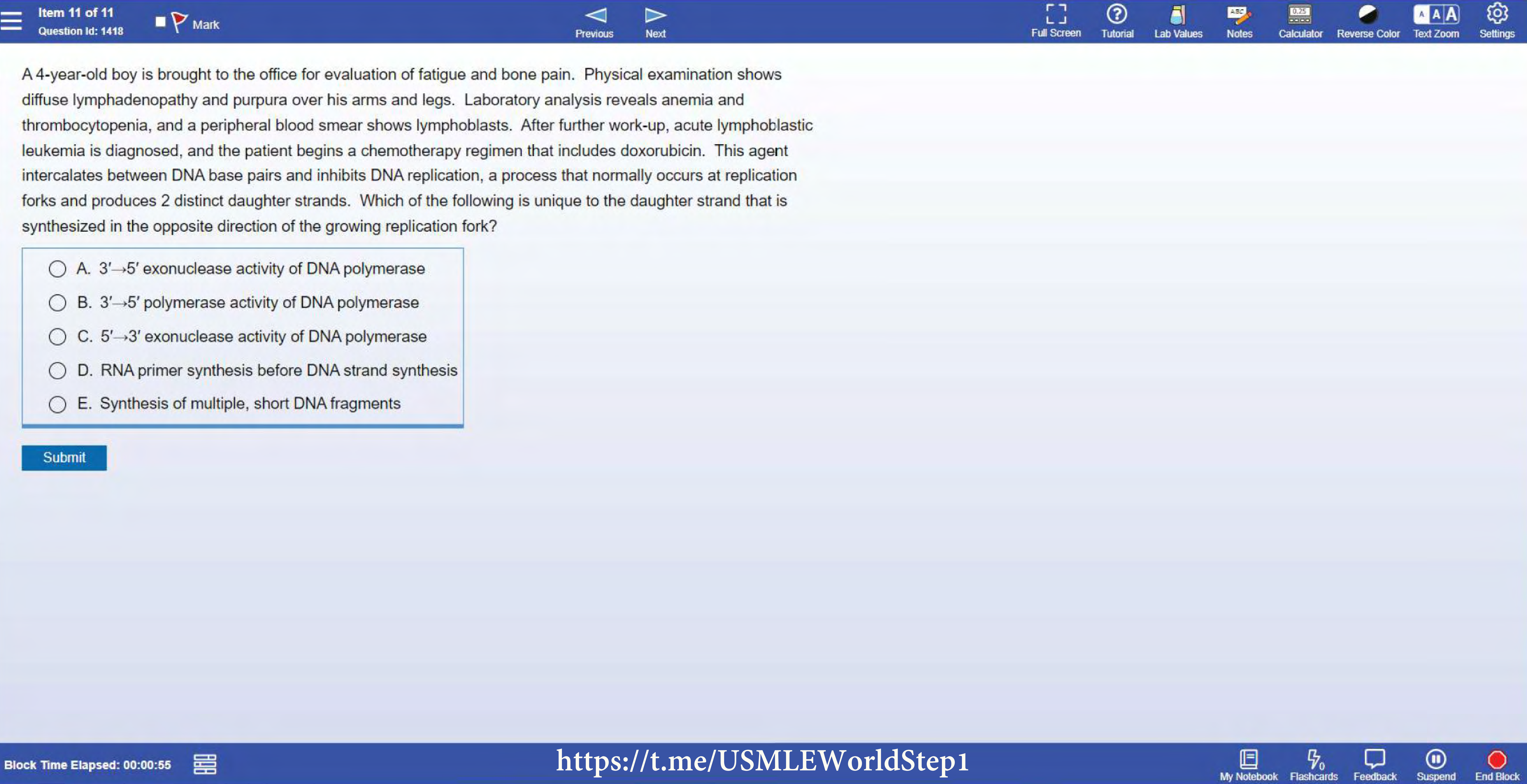
Explanation




Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 11 of 11
Question Id: 1418

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○ A. 3′→5′ exonuclease activity of DNA polymerase
○ B. 3′→5′ polymerase activity of DNA polymerase
○ C. 5′→3′ exonuclease activity of DNA polymerase
○ D. RNA primer synthesis before DNA strand synthesis
○ E. Synthesis of multiple, short DNA fragments

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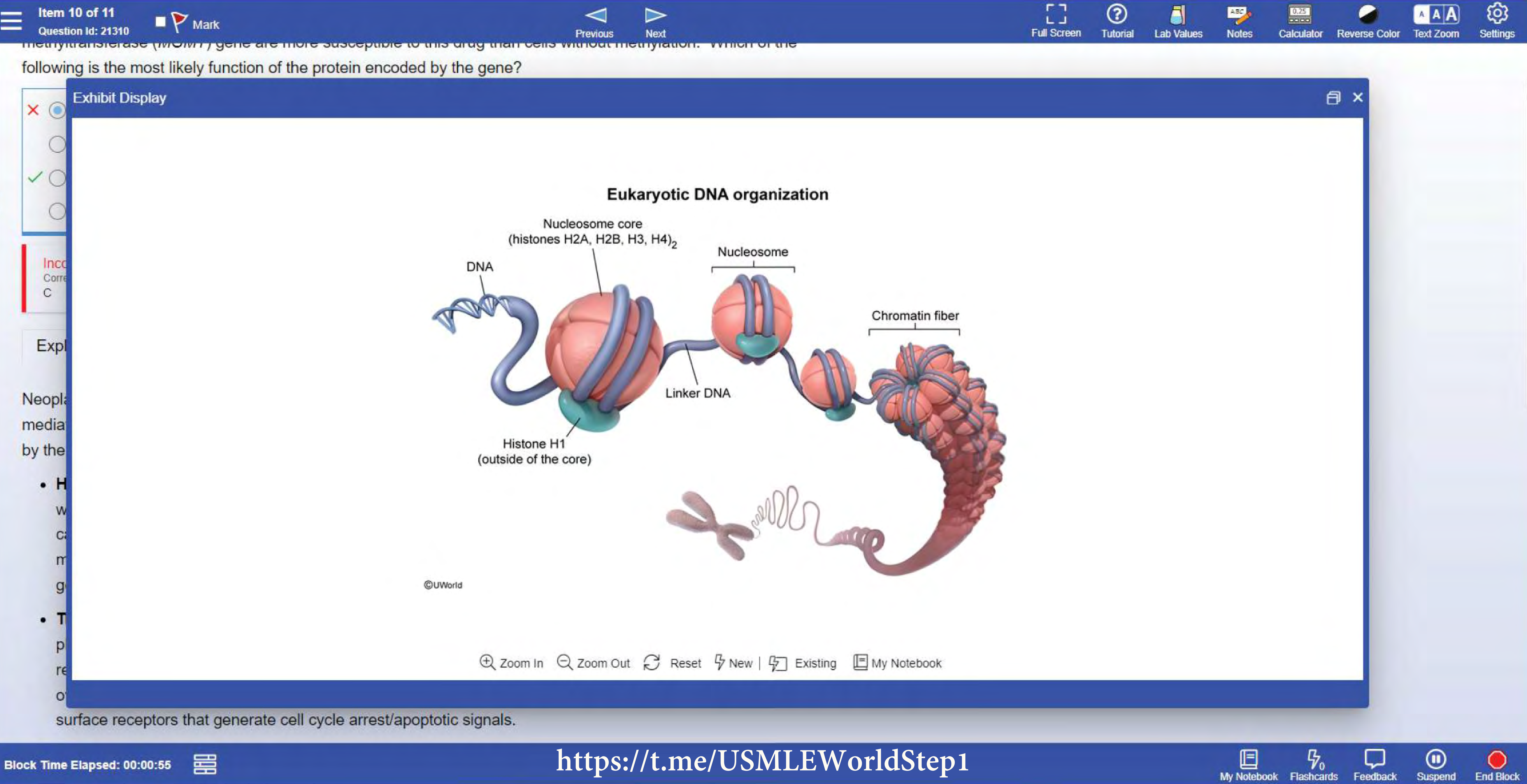
Item 10 of 11
Question Id: 21310
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

methyltransferase (MGMT) gene are more susceptible to this drug than cells without methylation. Which of the following is the most likely function of the protein encoded by the gene?

✗ ○
○
✓ ○
○

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surface receptors that generate cell cycle arrest/apoptotic signals.

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Eukaryotic DNA organization

Nucleosome core
(histones H2A, H2B, H3, H4)$_2$
DNA
Nucleosome
Chromatin fiber
Linker DNA
Histone H1
(outside of the core)
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My Notebook
Flashcards
Feedback
Suspend
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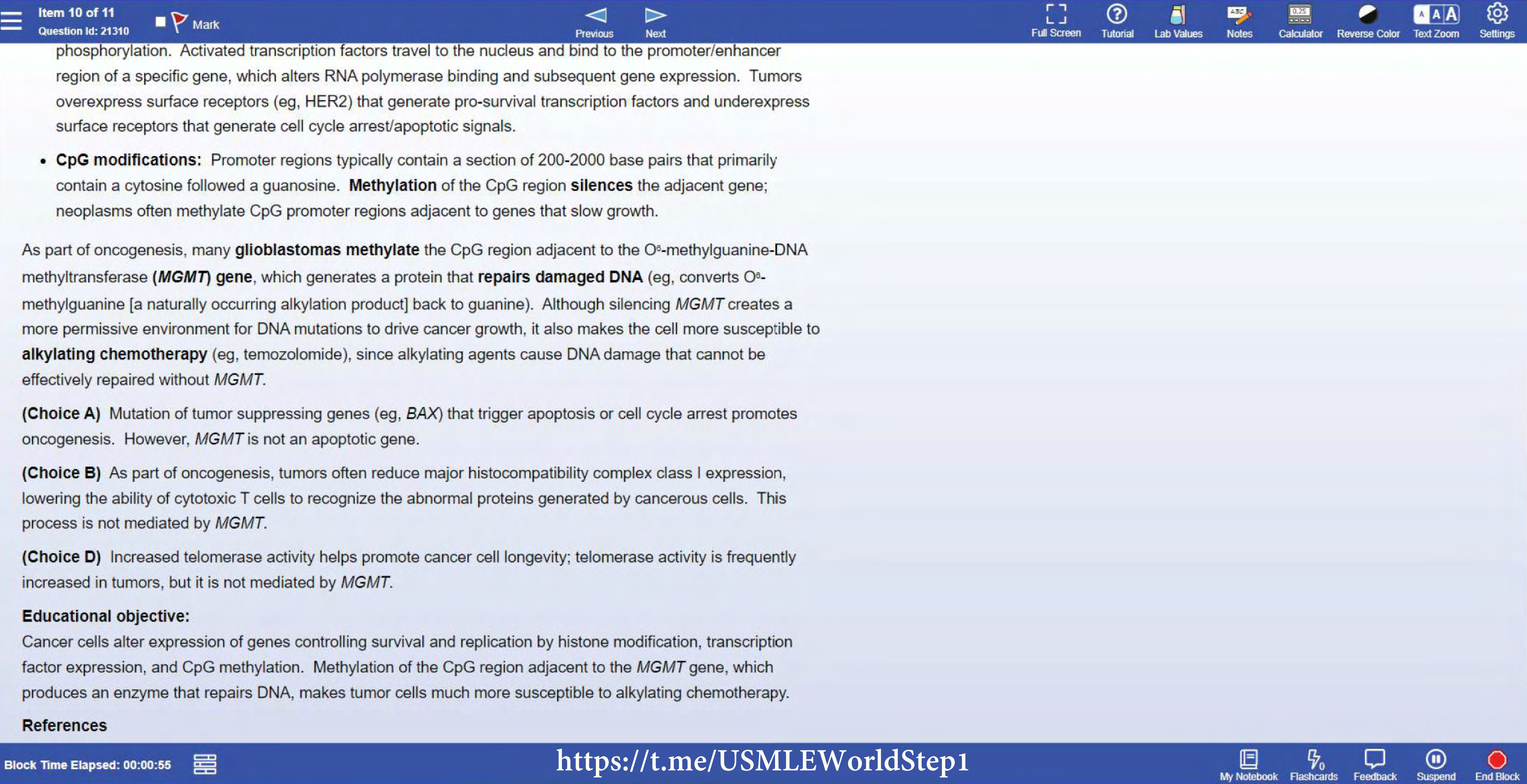


phosphorylation. Activated transcription factors travel to the nucleus and bind to the promoter/enhancer region of a specific gene, which alters RNA polymerase binding and subsequent gene expression. Tumors overexpress surface receptors (eg, HER2) that generate pro-survival transcription factors and underexpress surface receptors that generate cell cycle arrest/apoptotic signals.

- **CpG modifications:** Promoter regions typically contain a section of 200-2000 base pairs that primarily contain a cytosine followed a guanosine. **Methylation** of the CpG region **silences** the adjacent gene; neoplasms often methylate CpG promoter regions adjacent to genes that slow growth.

As part of oncogenesis, many **glioblastomas methylate** the CpG region adjacent to the O^6-methylguanine-DNA methyltransferase **(*MGMT*) gene**, which generates a protein that **repairs damaged DNA** (eg, converts O^6-methylguanine [a naturally occurring alkylation product] back to guanine). Although silencing *MGMT* creates a more permissive environment for DNA mutations to drive cancer growth, it also makes the cell more susceptible to **alkylating chemotherapy** (eg, temozolomide), since alkylating agents cause DNA damage that cannot be effectively repaired without *MGMT*.

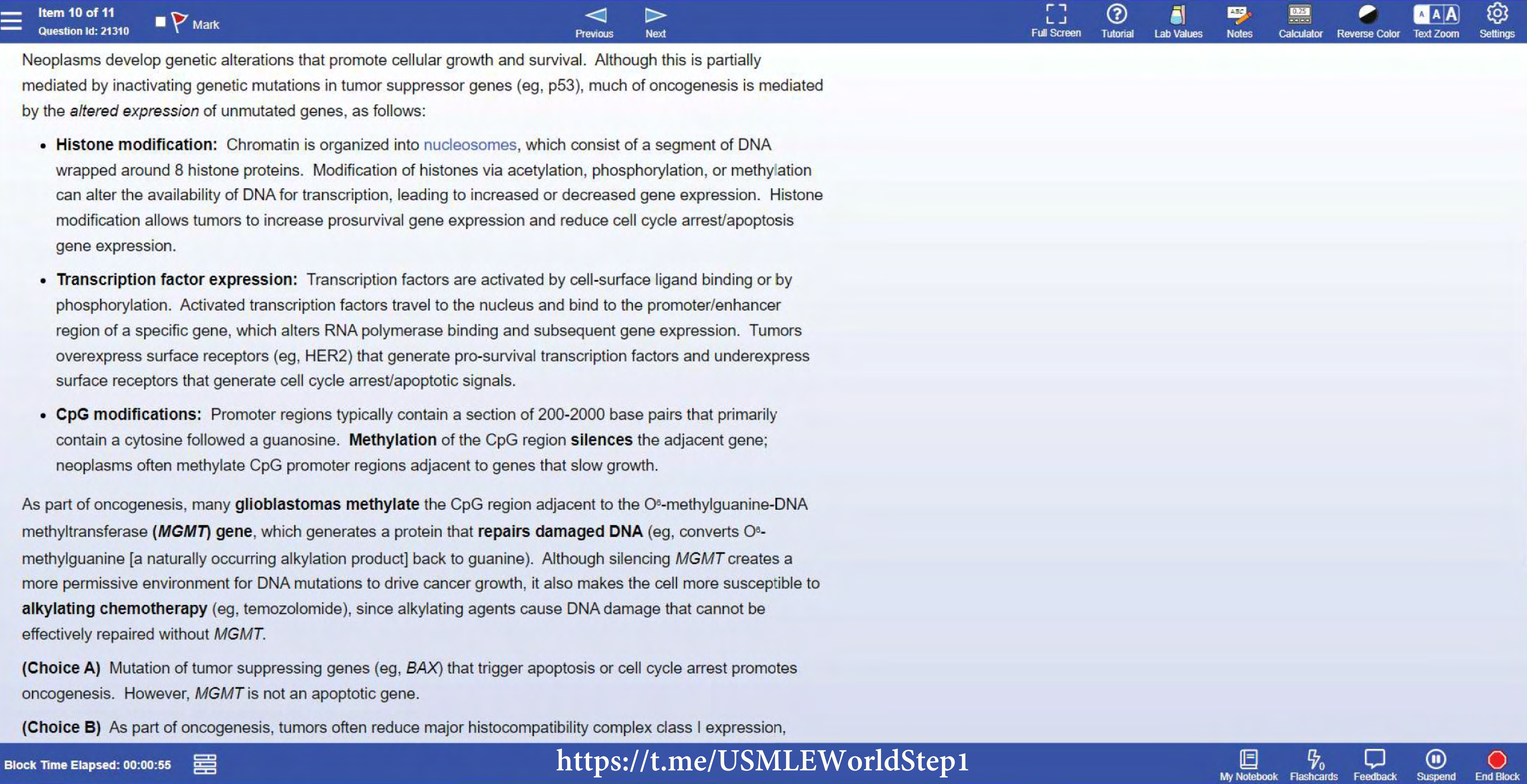
(Choice A) Mutation of tumor suppressing genes (eg, *BAX*) that trigger apoptosis or cell cycle arrest promotes oncogenesis. However, *MGMT* is not an apoptotic gene.

(Choice B) As part of oncogenesis, tumors often reduce major histocompatibility complex class I expression, lowering the ability of cytotoxic T cells to recognize the abnormal proteins generated by cancerous cells. This process is not mediated by *MGMT*.

(Choice D) Increased telomerase activity helps promote cancer cell longevity; telomerase activity is frequently increased in tumors, but it is not mediated by *MGMT*.

Educational objective:
Cancer cells alter expression of genes controlling survival and replication by histone modification, transcription factor expression, and CpG methylation. Methylation of the CpG region adjacent to the *MGMT* gene, which produces an enzyme that repairs DNA, makes tumor cells much more susceptible to alkylating chemotherapy.

References



Neoplasms develop genetic alterations that promote cellular growth and survival. Although this is partially mediated by inactivating genetic mutations in tumor suppressor genes (eg, p53), much of oncogenesis is mediated by the *altered expression* of unmutated genes, as follows:

- **Histone modification:** Chromatin is organized into nucleosomes, which consist of a segment of DNA wrapped around 8 histone proteins. Modification of histones via acetylation, phosphorylation, or methylation can alter the availability of DNA for transcription, leading to increased or decreased gene expression. Histone modification allows tumors to increase prosurvival gene expression and reduce cell cycle arrest/apoptosis gene expression.
- **Transcription factor expression:** Transcription factors are activated by cell-surface ligand binding or by phosphorylation. Activated transcription factors travel to the nucleus and bind to the promoter/enhancer region of a specific gene, which alters RNA polymerase binding and subsequent gene expression. Tumors overexpress surface receptors (eg, HER2) that generate pro-survival transcription factors and underexpress surface receptors that generate cell cycle arrest/apoptotic signals.
- **CpG modifications:** Promoter regions typically contain a section of 200-2000 base pairs that primarily contain a cytosine followed a guanosine. **Methylation** of the CpG region **silences** the adjacent gene; neoplasms often methylate CpG promoter regions adjacent to genes that slow growth.

As part of oncogenesis, many **glioblastomas methylate** the CpG region adjacent to the O^6-methylguanine-DNA methyltransferase **(*MGMT*) gene**, which generates a protein that **repairs damaged DNA** (eg, converts O^6-methylguanine [a naturally occurring alkylation product] back to guanine). Although silencing *MGMT* creates a more permissive environment for DNA mutations to drive cancer growth, it also makes the cell more susceptible to **alkylating chemotherapy** (eg, temozolomide), since alkylating agents cause DNA damage that cannot be effectively repaired without *MGMT*.

(Choice A) Mutation of tumor suppressing genes (eg, *BAX*) that trigger apoptosis or cell cycle arrest promotes oncogenesis. However, *MGMT* is not an apoptotic gene.

(Choice B) As part of oncogenesis, tumors often reduce major histocompatibility complex class I expression,

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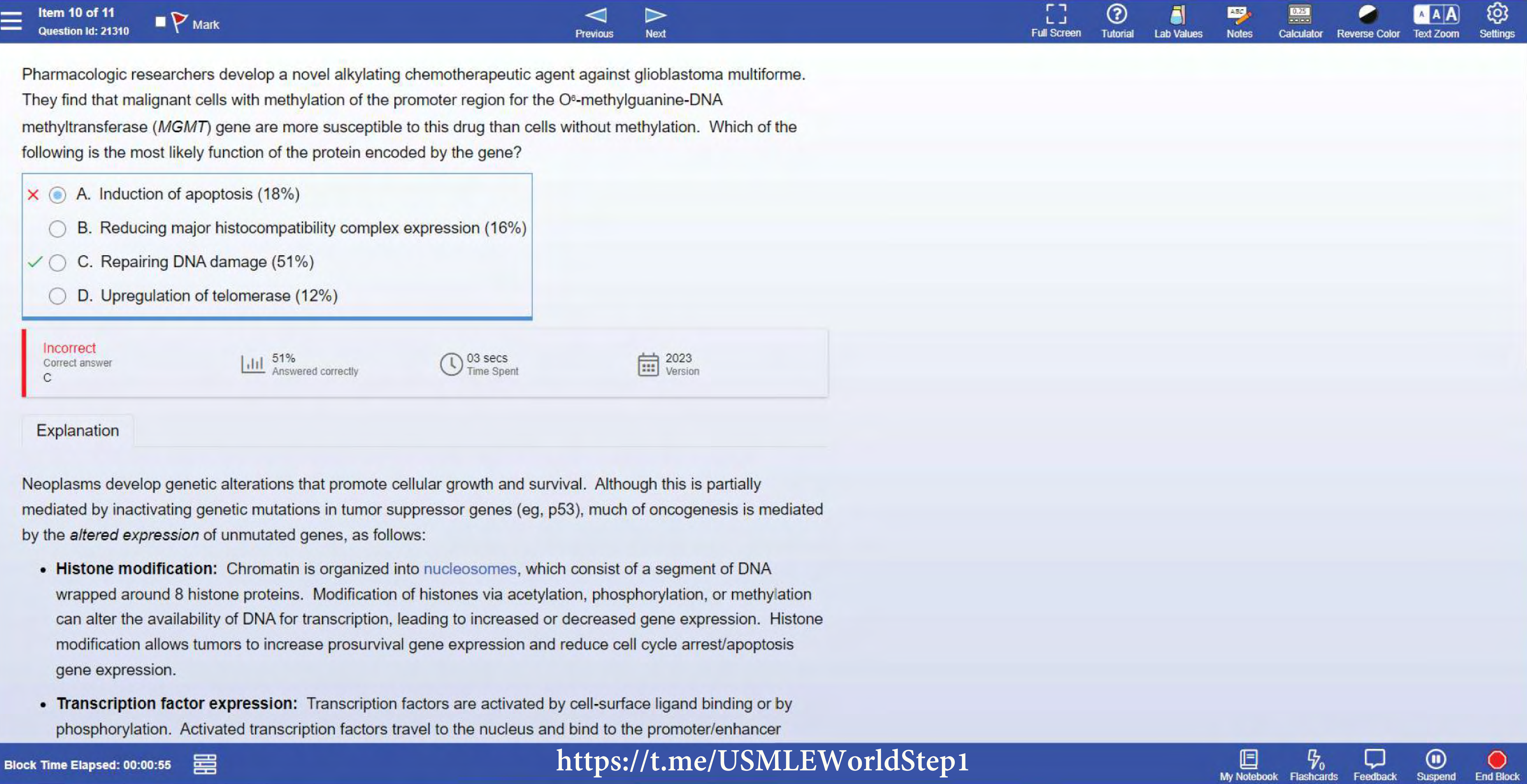
Item 10 of 11
Question Id: 21310
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Pharmacologic researchers develop a novel alkylating chemotherapeutic agent against glioblastoma multiforme. They find that malignant cells with methylation of the promoter region for the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene are more susceptible to this drug than cells without methylation. Which of the following is the most likely function of the protein encoded by the gene?

✗ ● A. Induction of apoptosis (18%)

○ B. Reducing major histocompatibility complex expression (16%)

✓ ○ C. Repairing DNA damage (51%)

○ D. Upregulation of telomerase (12%)

Incorrect
Correct answer
C

51%
Answered correctly

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Explanation

Neoplasms develop genetic alterations that promote cellular growth and survival. Although this is partially mediated by inactivating genetic mutations in tumor suppressor genes (eg, p53), much of oncogenesis is mediated by the *altered expression* of unmutated genes, as follows:

- **Histone modification:** Chromatin is organized into nucleosomes, which consist of a segment of DNA wrapped around 8 histone proteins. Modification of histones via acetylation, phosphorylation, or methylation can alter the availability of DNA for transcription, leading to increased or decreased gene expression. Histone modification allows tumors to increase prosurvival gene expression and reduce cell cycle arrest/apoptosis gene expression.
- **Transcription factor expression:** Transcription factors are activated by cell-surface ligand binding or by phosphorylation. Activated transcription factors travel to the nucleus and bind to the promoter/enhancer

Block Time Elapsed: 00:00:55
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 10 of 11
Question Id: 21310
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:00:52
My Notebook
Flashcards
Feedback
Suspend
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- ○ C. Repairing DNA damage
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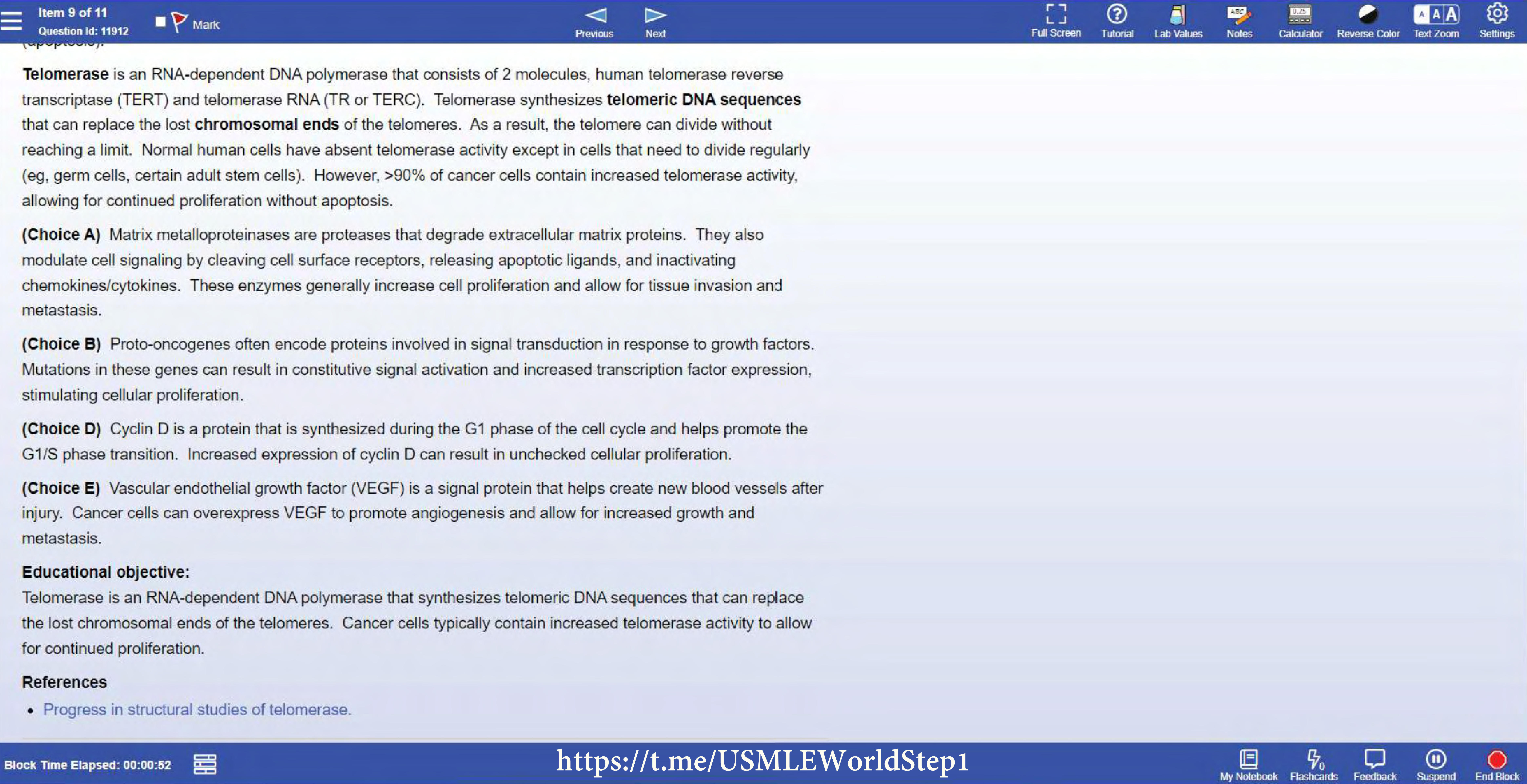


Telomerase is an RNA-dependent DNA polymerase that consists of 2 molecules, human telomerase reverse transcriptase (TERT) and telomerase RNA (TR or TERC). Telomerase synthesizes **telomeric DNA sequences** that can replace the lost **chromosomal ends** of the telomeres. As a result, the telomere can divide without reaching a limit. Normal human cells have absent telomerase activity except in cells that need to divide regularly (eg, germ cells, certain adult stem cells). However, >90% of cancer cells contain increased telomerase activity, allowing for continued proliferation without apoptosis.

(Choice A) Matrix metalloproteinases are proteases that degrade extracellular matrix proteins. They also modulate cell signaling by cleaving cell surface receptors, releasing apoptotic ligands, and inactivating chemokines/cytokines. These enzymes generally increase cell proliferation and allow for tissue invasion and metastasis.

(Choice B) Proto-oncogenes often encode proteins involved in signal transduction in response to growth factors. Mutations in these genes can result in constitutive signal activation and increased transcription factor expression, stimulating cellular proliferation.

(Choice D) Cyclin D is a protein that is synthesized during the G1 phase of the cell cycle and helps promote the G1/S phase transition. Increased expression of cyclin D can result in unchecked cellular proliferation.

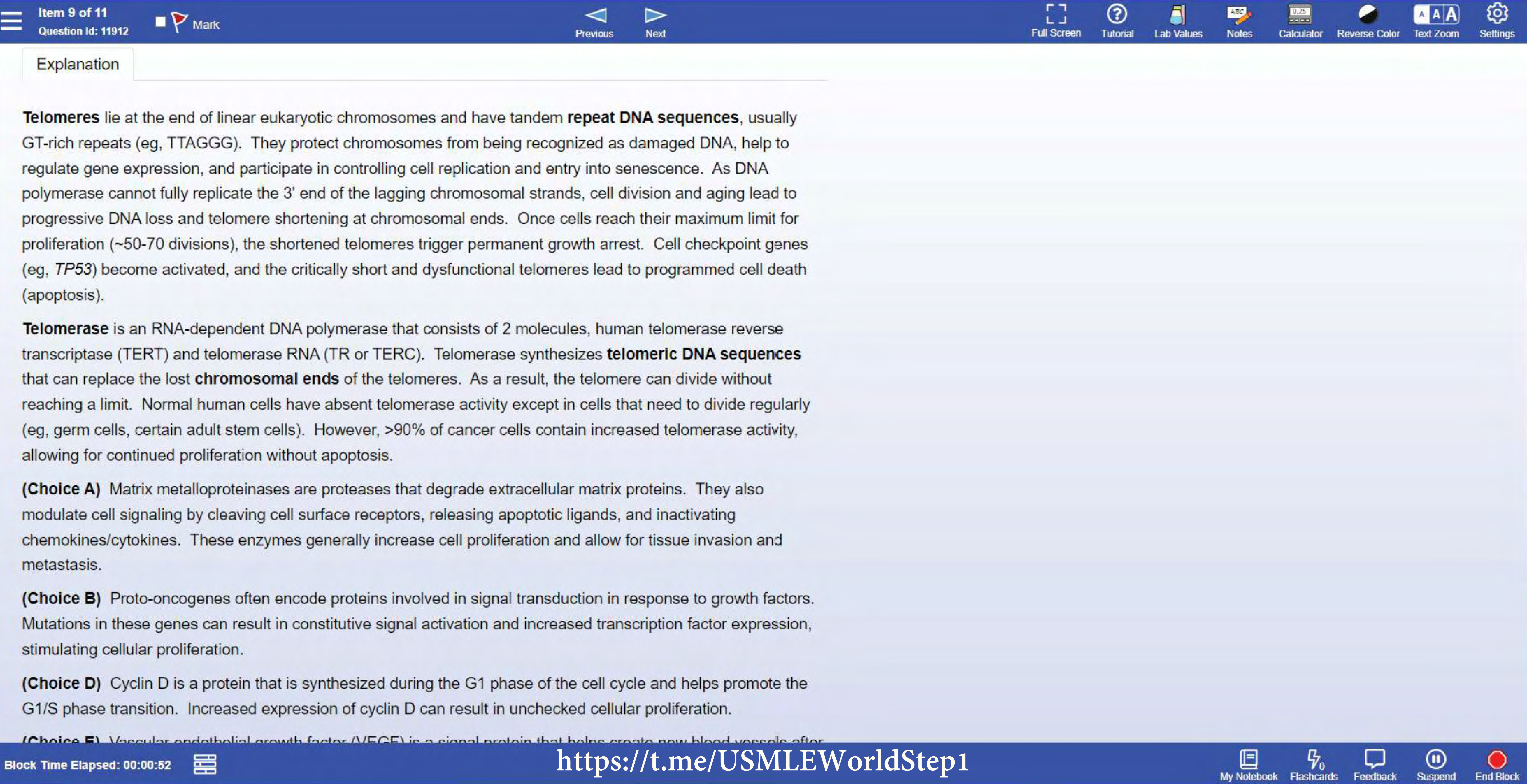
(Choice E) Vascular endothelial growth factor (VEGF) is a signal protein that helps create new blood vessels after injury. Cancer cells can overexpress VEGF to promote angiogenesis and allow for increased growth and metastasis.

Educational objective:

Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences that can replace the lost chromosomal ends of the telomeres. Cancer cells typically contain increased telomerase activity to allow for continued proliferation.

References

- Progress in structural studies of telomerase.



Telomeres lie at the end of linear eukaryotic chromosomes and have tandem **repeat DNA sequences**, usually GT-rich repeats (eg, TTAGGG). They protect chromosomes from being recognized as damaged DNA, help to regulate gene expression, and participate in controlling cell replication and entry into senescence. As DNA polymerase cannot fully replicate the 3' end of the lagging chromosomal strands, cell division and aging lead to progressive DNA loss and telomere shortening at chromosomal ends. Once cells reach their maximum limit for proliferation (~50-70 divisions), the shortened telomeres trigger permanent growth arrest. Cell checkpoint genes (eg, *TP53*) become activated, and the critically short and dysfunctional telomeres lead to programmed cell death (apoptosis).

Telomerase is an RNA-dependent DNA polymerase that consists of 2 molecules, human telomerase reverse transcriptase (TERT) and telomerase RNA (TR or TERC). Telomerase synthesizes **telomeric DNA sequences** that can replace the lost **chromosomal ends** of the telomeres. As a result, the telomere can divide without reaching a limit. Normal human cells have absent telomerase activity except in cells that need to divide regularly (eg, germ cells, certain adult stem cells). However, >90% of cancer cells contain increased telomerase activity, allowing for continued proliferation without apoptosis.

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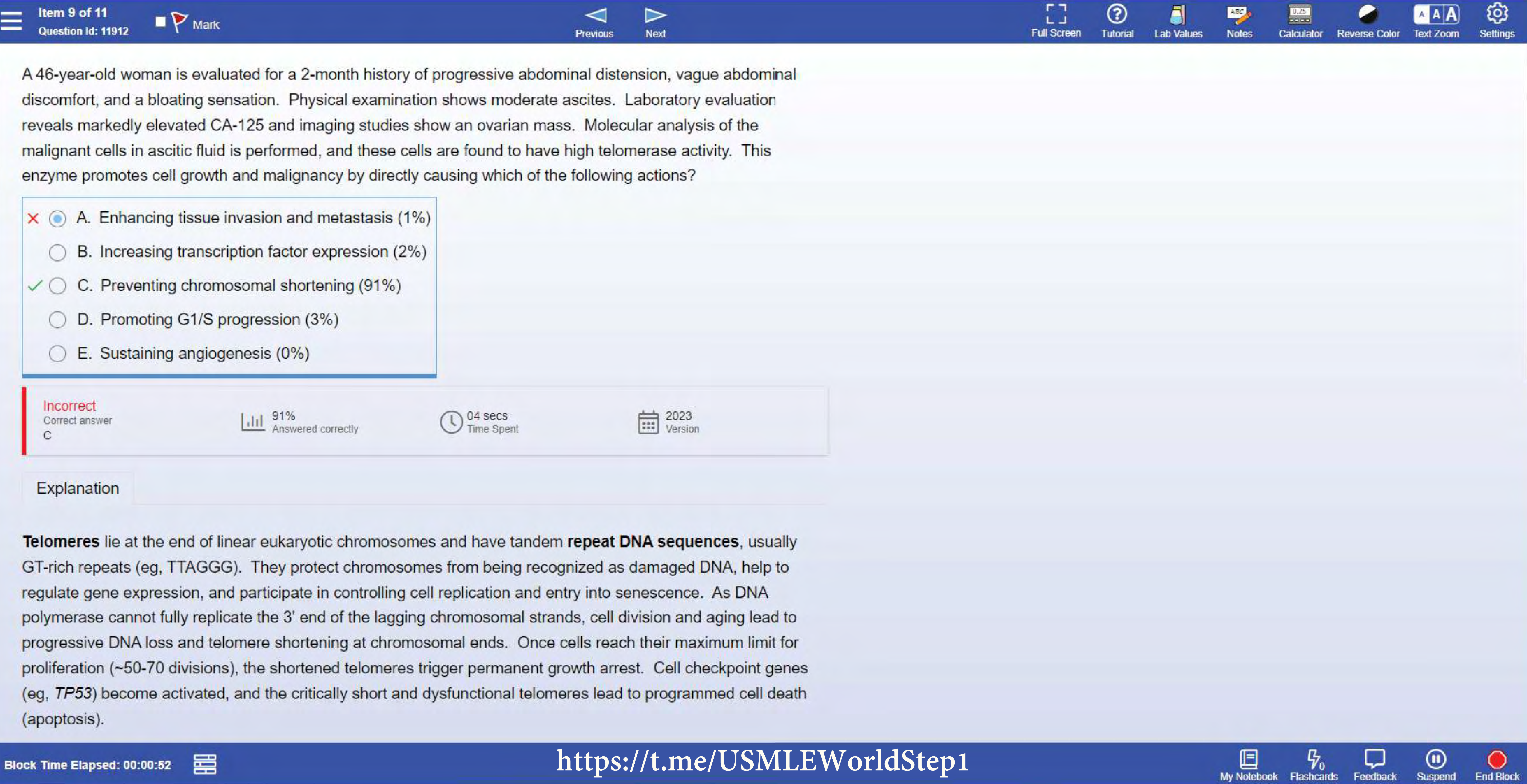
Item 9 of 11
Question Id: 11912
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 46-year-old woman is evaluated for a 2-month history of progressive abdominal distension, vague abdominal discomfort, and a bloating sensation. Physical examination shows moderate ascites. Laboratory evaluation reveals markedly elevated CA-125 and imaging studies show an ovarian mass. Molecular analysis of the malignant cells in ascitic fluid is performed, and these cells are found to have high telomerase activity. This enzyme promotes cell growth and malignancy by directly causing which of the following actions?

- ✗ ● A. Enhancing tissue invasion and metastasis (1%)
- ○ B. Increasing transcription factor expression (2%)
- ✓ ○ C. Preventing chromosomal shortening (91%)
- ○ D. Promoting G1/S progression (3%)
- ○ E. Sustaining angiogenesis (0%)

Incorrect
Correct answer
C

91%
Answered correctly

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Explanation

Telomeres lie at the end of linear eukaryotic chromosomes and have tandem **repeat DNA sequences**, usually GT-rich repeats (eg, TTAGGG). They protect chromosomes from being recognized as damaged DNA, help to regulate gene expression, and participate in controlling cell replication and entry into senescence. As DNA polymerase cannot fully replicate the 3' end of the lagging chromosomal strands, cell division and aging lead to progressive DNA loss and telomere shortening at chromosomal ends. Once cells reach their maximum limit for proliferation (~50-70 divisions), the shortened telomeres trigger permanent growth arrest. Cell checkpoint genes (eg, *TP53*) become activated, and the critically short and dysfunctional telomeres lead to programmed cell death (apoptosis).

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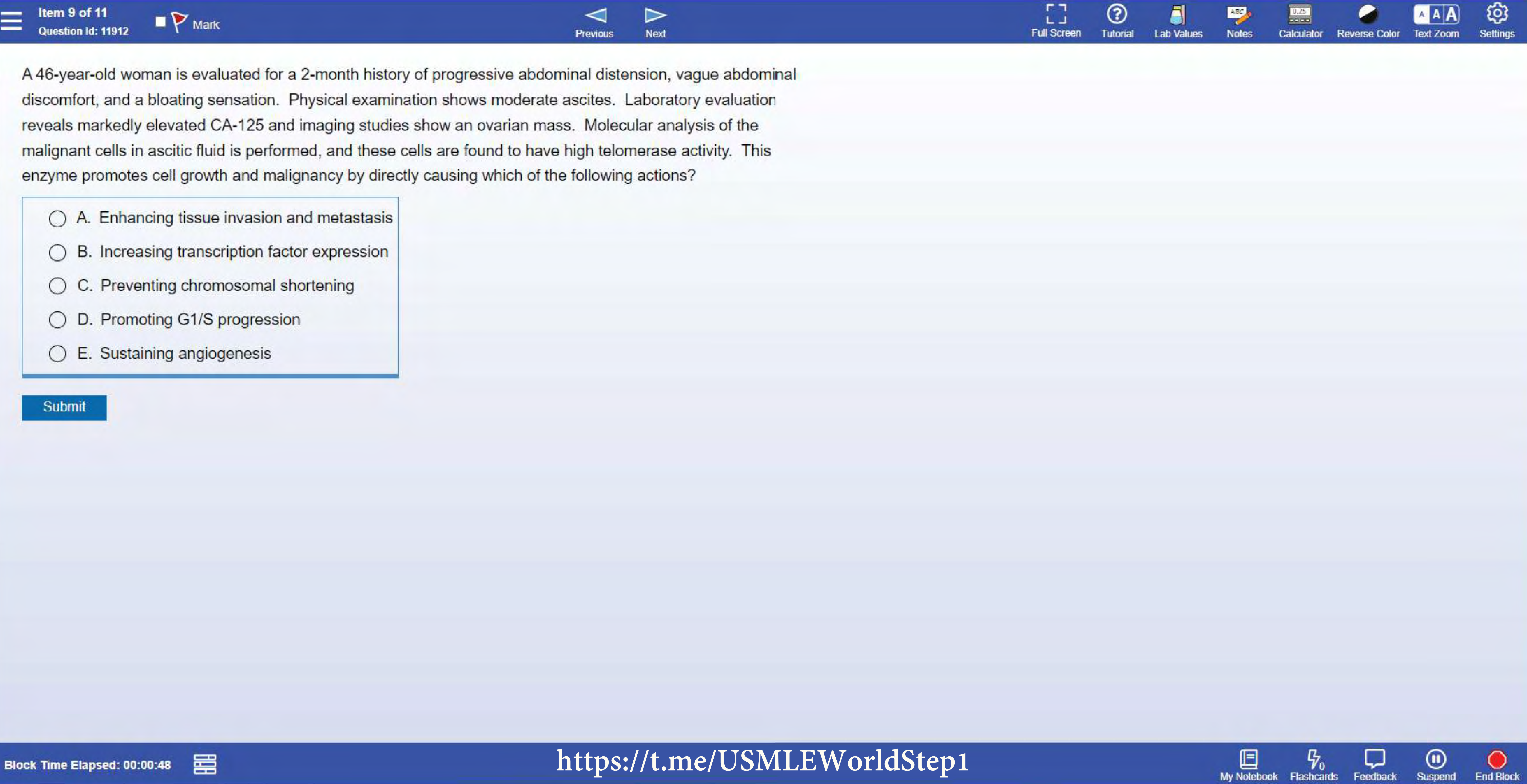
Item 9 of 11
Question Id: 11912
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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- ○ C. Preventing chromosomal shortening
- ○ D. Promoting G1/S progression
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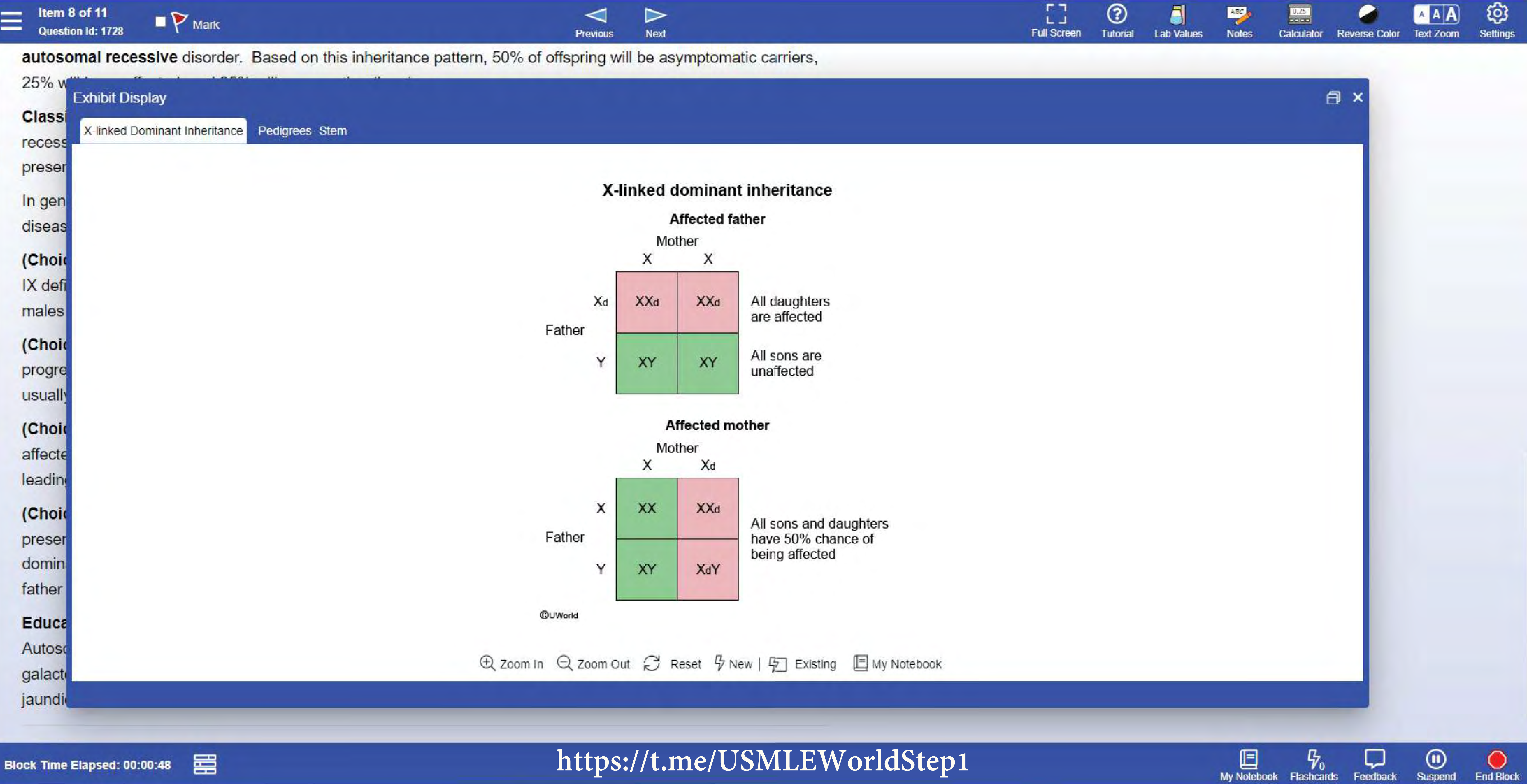
Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Exhibit Display
X-linked Dominant Inheritance
Pedigrees- Stem

X-linked dominant inheritance

Affected father

		Mother X	Mother X	
Father	X_d	XX_d	XX_d	All daughters are affected
Father	Y	XY	XY	All sons are unaffected

Affected mother

		Mother X	Mother X_d	
Father	X	XX	XX_d	All sons and daughters have 50% chance of being affected
Father	Y	XY	X_dY	

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Feedback
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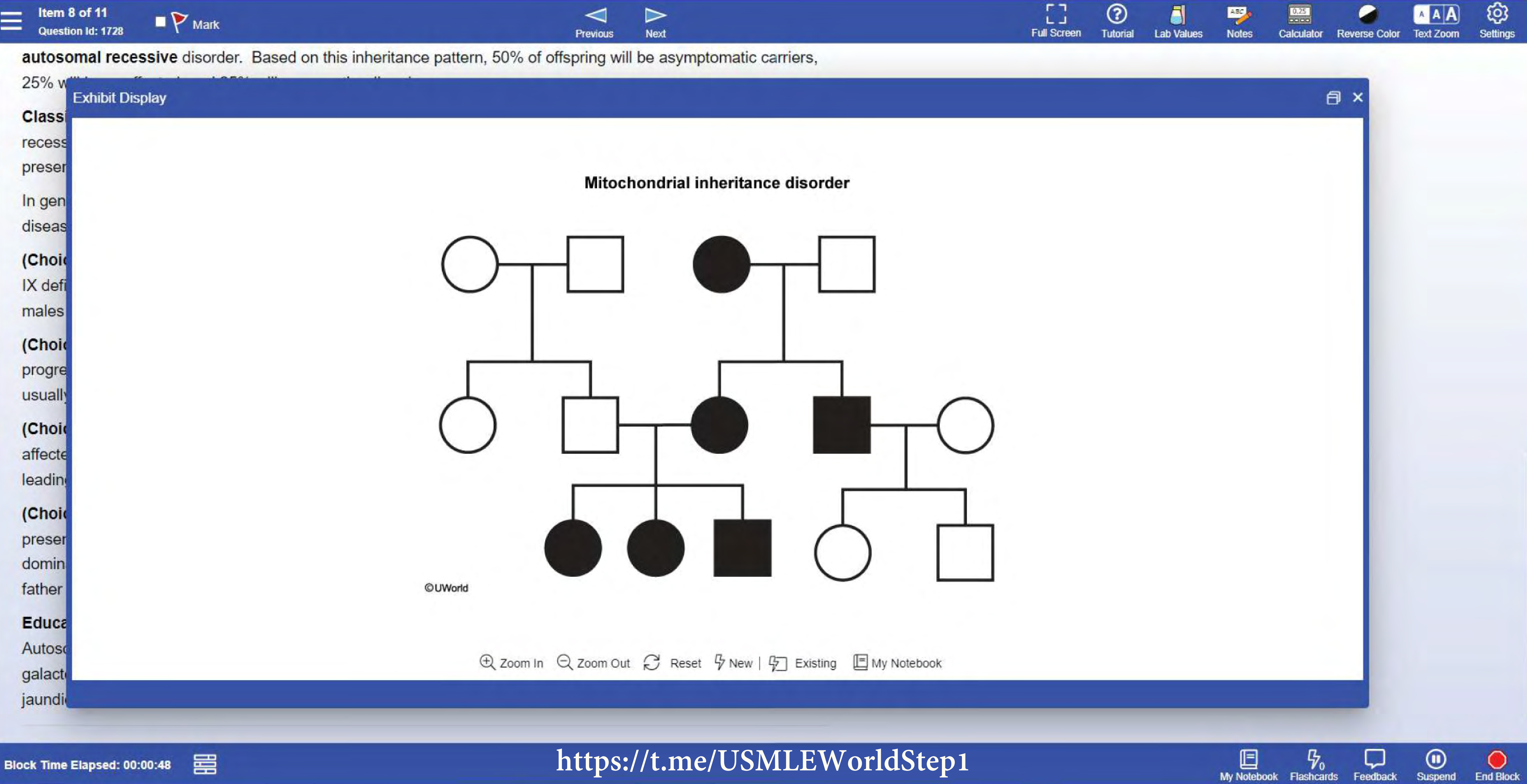
Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
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Text Zoom
Settings
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Zoom Out
Reset
New
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Block Time Elapsed: 00:00:48
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Mitochondrial inheritance disorder

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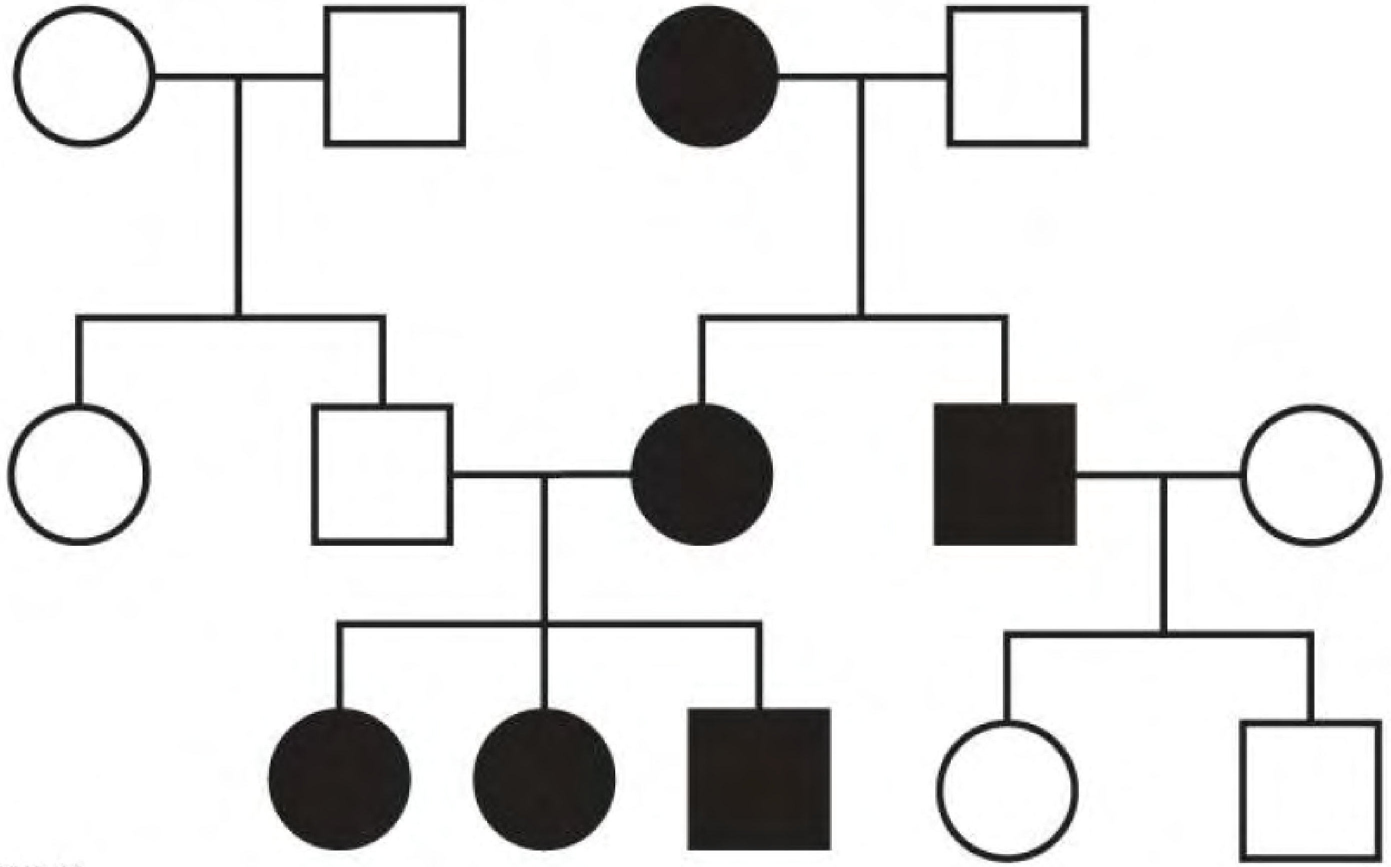
Mitochondrial inheritance disorder



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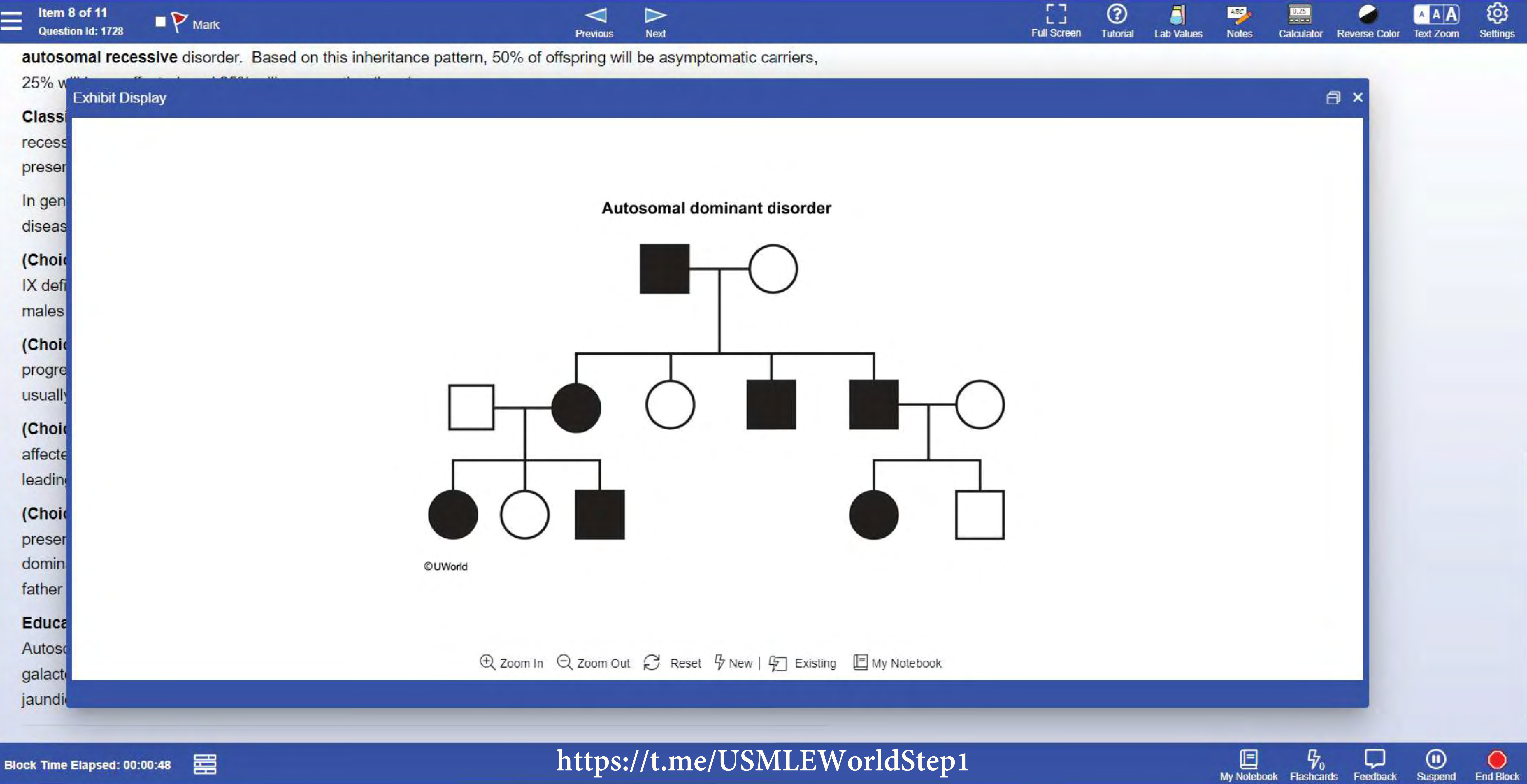
Item 8 of 11
Question Id: 1728
Mark
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Autosomal dominant disorder

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Zoom In
Zoom Out
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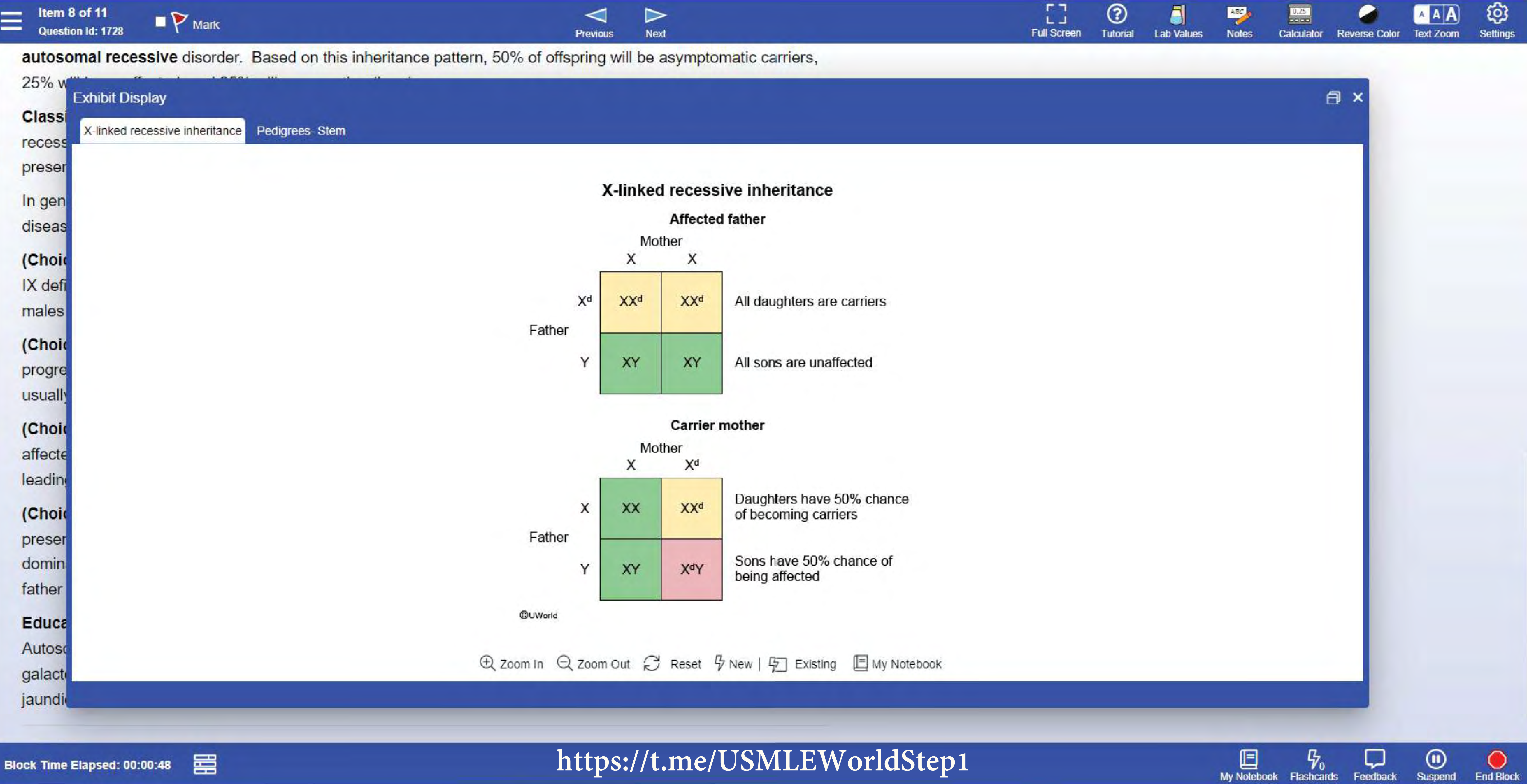
My Notebook

Block Time Elapsed: 00:00:48

My Notebook
Flashcards
Feedback
Suspend
End Block


Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
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Exhibit Display
X-linked recessive inheritance
Pedigrees- Stem

X-linked recessive inheritance

Affected father

Father \ Mother	X	X	
X^d	XX^d	XX^d	All daughters are carriers
Y	XY	XY	All sons are unaffected

Carrier mother

Father \ Mother	X	X^d	
X	XX	XX^d	Daughters have 50% chance of becoming carriers
Y	XY	X^dY	Sons have 50% chance of being affected

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Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:00:48

My Notebook
Flashcards
Feedback
Suspend
End Block

Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:00:48
My Notebook
Flashcards
Feedback
Suspend
End Block

autosomal recessive disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

Classic galactosemia is the most common and most severe of the galactosemic disorders. It is an autosomal recessive disorder leading to complete enzymatic absence of galactose-1-phosphate uridyl transferase. Newborns present within days of birth with jaundice, vomiting, and hepatomegaly.

In general, most **enzyme deficiency conditions** follow an autosomal recessive inheritance pattern whereas diseases due to defective noncatalytic proteins follow an autosomal dominant pattern.

(Choice B) Hemophilia B (Christmas disease) is an X-linked recessive disorder affecting **males** that causes factor IX deficiency with easy bruising and bleeding (eg, hemarthrosis, oral bleeding, intracranial hemorrhage). Affected males will have asymptomatic carrier mothers.

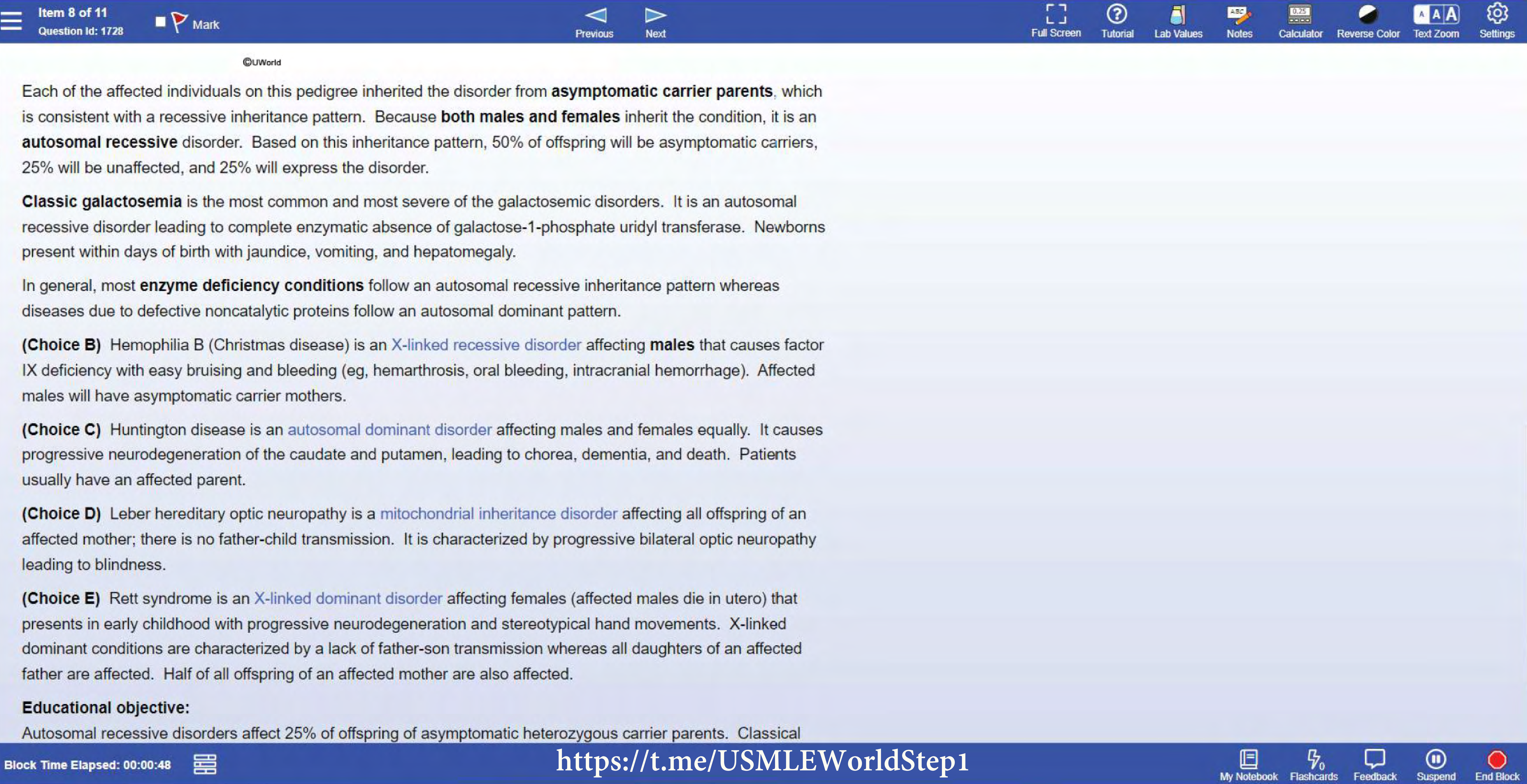
(Choice C) Huntington disease is an autosomal dominant disorder affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and death. Patients usually have an affected parent.

(Choice D) Leber hereditary optic neuropathy is a mitochondrial inheritance disorder affecting all offspring of an affected mother; there is no father-child transmission. It is characterized by progressive bilateral optic neuropathy leading to blindness.

(Choice E) Rett syndrome is an X-linked dominant disorder affecting females (affected males die in utero) that presents in early childhood with progressive neurodegeneration and stereotypical hand movements. X-linked dominant conditions are characterized by a lack of father-son transmission whereas all daughters of an affected father are affected. Half of all offspring of an affected mother are also affected.

Educational objective:

Autosomal recessive disorders affect 25% of offspring of asymptomatic heterozygous carrier parents. Classical galactosemia is the most common and severe galactosemic disorder and presents within days of birth with jaundice, vomiting, and hepatomegaly.



Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive inheritance pattern. Because **both males and females** inherit the condition, it is an **autosomal recessive** disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

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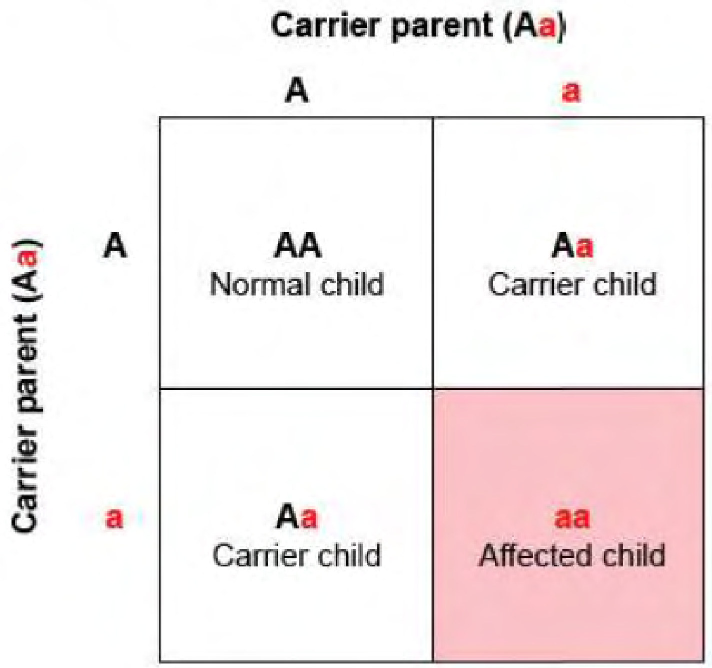
Educational objective:

Autosomal recessive disorders affect 25% of offspring of asymptomatic heterozygous carrier parents. Classical

Autosomal recessive inheritance

Exhibit Display

Autosomal recessive inheritance


Carrier parent (Aa)
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Offspring have 25% chance of being affected

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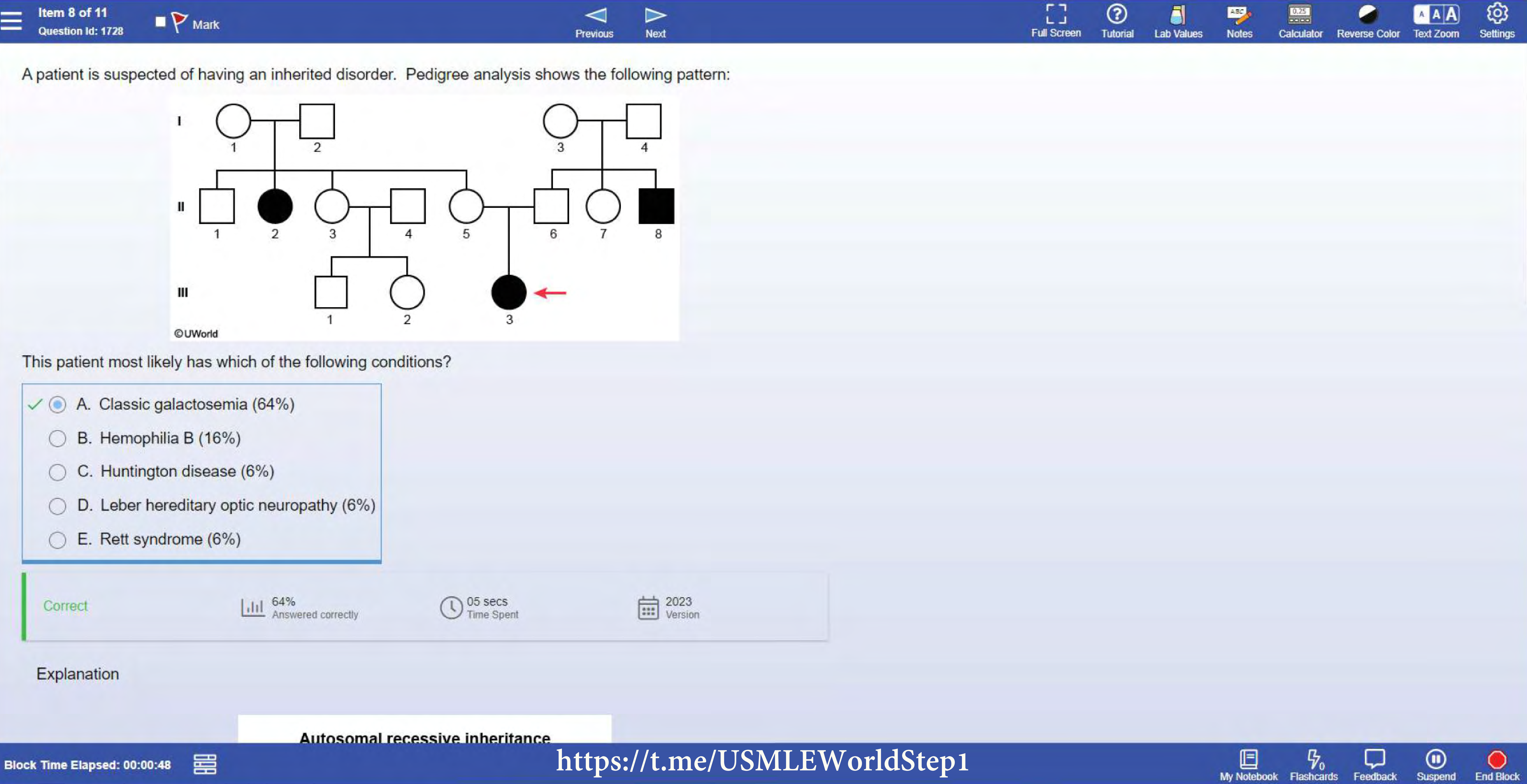
Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A patient is suspected of having an inherited disorder. Pedigree analysis shows the following pattern:

I
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This patient most likely has which of the following conditions?

✓ ● A. Classic galactosemia (64%)

○ B. Hemophilia B (16%)

○ C. Huntington disease (6%)

○ D. Leber hereditary optic neuropathy (6%)

○ E. Rett syndrome (6%)

Correct

64% Answered correctly

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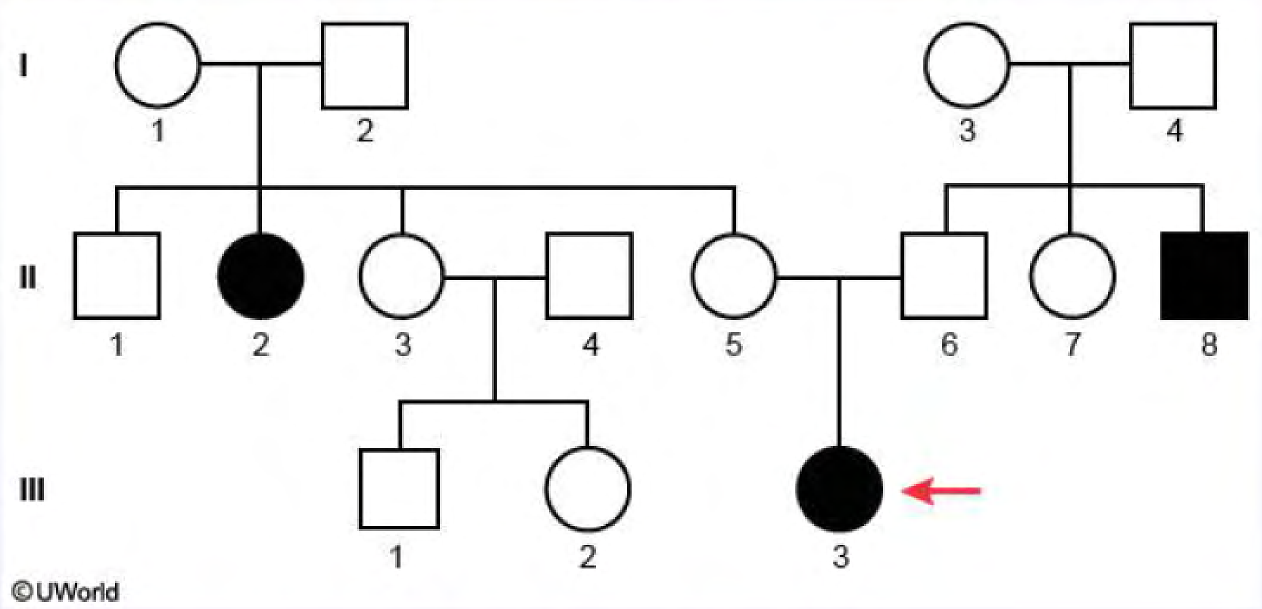
2023 Version

Explanation

Autosomal recessive inheritance

Block Time Elapsed: 00:00:48
My Notebook
Flashcards
Feedback
Suspend
End Block

A patient is suspected of having an inherited disorder. Pedigree analysis shows the following pattern:



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○ B. Hemophilia B

○ C. Huntington disease

○ D. Leber hereditary optic neuropathy

○ E. Rett syndrome

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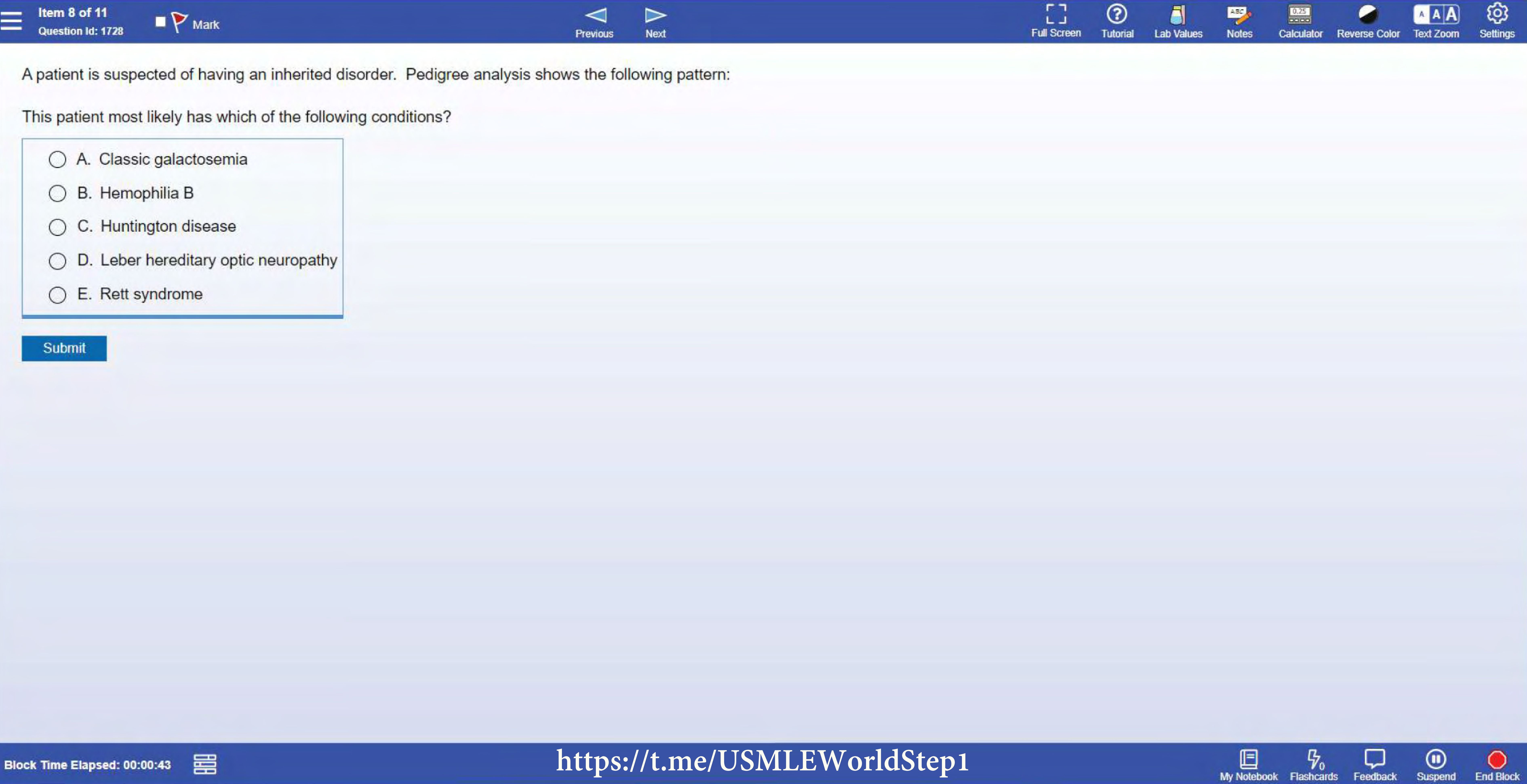
Item 8 of 11
Question Id: 1728
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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This patient most likely has which of the following conditions?

○ A. Classic galactosemia
○ B. Hemophilia B
○ C. Huntington disease
○ D. Leber hereditary optic neuropathy
○ E. Rett syndrome

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Block Time Elapsed: 00:00:43
My Notebook
Flashcards
Feedback
Suspend
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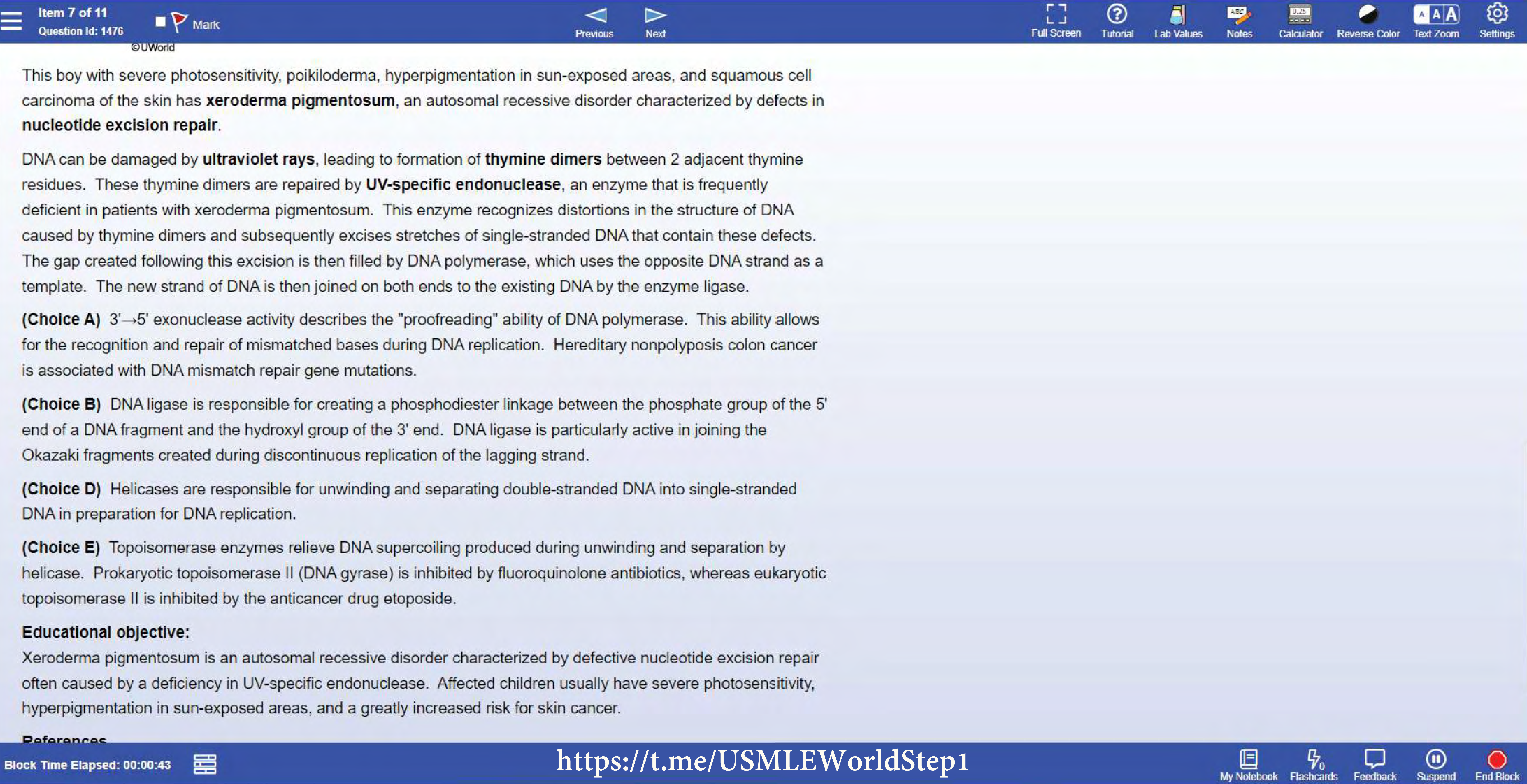

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This boy with severe photosensitivity, poikiloderma, hyperpigmentation in sun-exposed areas, and squamous cell carcinoma of the skin has **xeroderma pigmentosum**, an autosomal recessive disorder characterized by defects in **nucleotide excision repair**.

DNA can be damaged by **ultraviolet rays**, leading to formation of **thymine dimers** between 2 adjacent thymine residues. These thymine dimers are repaired by **UV-specific endonuclease**, an enzyme that is frequently deficient in patients with xeroderma pigmentosum. This enzyme recognizes distortions in the structure of DNA caused by thymine dimers and subsequently excises stretches of single-stranded DNA that contain these defects. The gap created following this excision is then filled by DNA polymerase, which uses the opposite DNA strand as a template. The new strand of DNA is then joined on both ends to the existing DNA by the enzyme ligase.

(Choice A) 3'→5' exonuclease activity describes the "proofreading" ability of DNA polymerase. This ability allows for the recognition and repair of mismatched bases during DNA replication. Hereditary nonpolyposis colon cancer is associated with DNA mismatch repair gene mutations.

(Choice B) DNA ligase is responsible for creating a phosphodiester linkage between the phosphate group of the 5' end of a DNA fragment and the hydroxyl group of the 3' end. DNA ligase is particularly active in joining the Okazaki fragments created during discontinuous replication of the lagging strand.

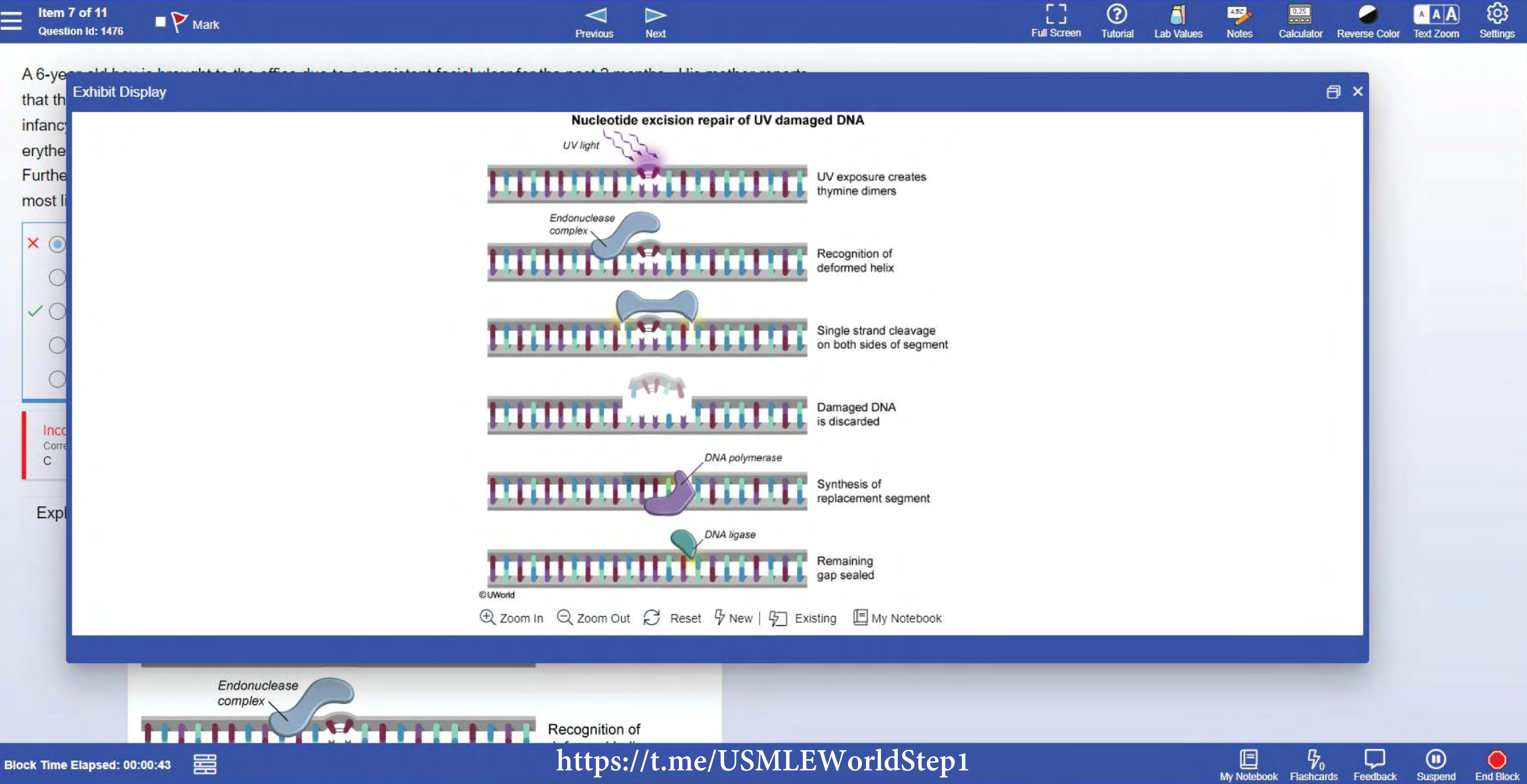
(Choice D) Helicases are responsible for unwinding and separating double-stranded DNA into single-stranded DNA in preparation for DNA replication.

(Choice E) Topoisomerase enzymes relieve DNA supercoiling produced during unwinding and separation by helicase. Prokaryotic topoisomerase II (DNA gyrase) is inhibited by fluoroquinolone antibiotics, whereas eukaryotic topoisomerase II is inhibited by the anticancer drug etoposide.

Educational objective:

Xeroderma pigmentosum is an autosomal recessive disorder characterized by defective nucleotide excision repair often caused by a deficiency in UV-specific endonuclease. Affected children usually have severe photosensitivity, hyperpigmentation in sun-exposed areas, and a greatly increased risk for skin cancer.

References


Item 7 of 11
Question Id: 1476
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Previous
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Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Nucleotide excision repair of UV damaged DNA

UV light
UV exposure creates thymine dimers
Endonuclease complex
Recognition of deformed helix
Single strand cleavage on both sides of segment
Damaged DNA is discarded
DNA polymerase
Synthesis of replacement segment
DNA ligase
Remaining gap sealed

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My Notebook
Flashcards
Feedback
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A 6-year-old boy is brought to the office due to a persistent facial ulcer for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

✗ ● A. 3'→5' exonuclease (33%)
○ B. DNA ligase (4%)
✓ ○ C. Endonuclease (58%)
○ D. Helicase (0%)
○ E. Topoisomerase (2%)

Incorrect
Correct answer
C

58%
Answered correctly

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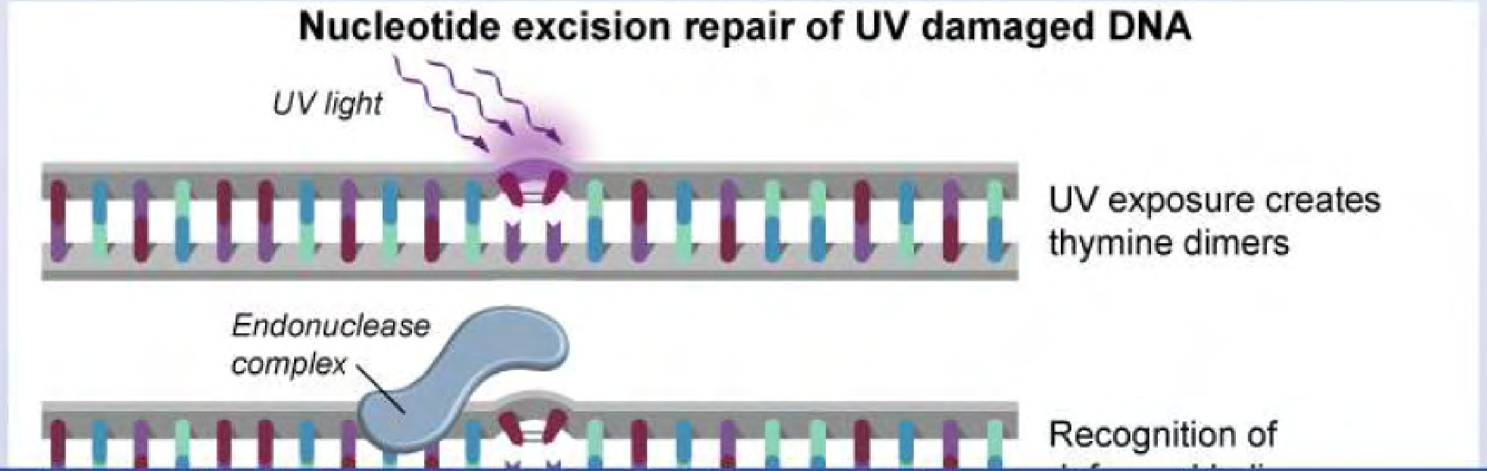
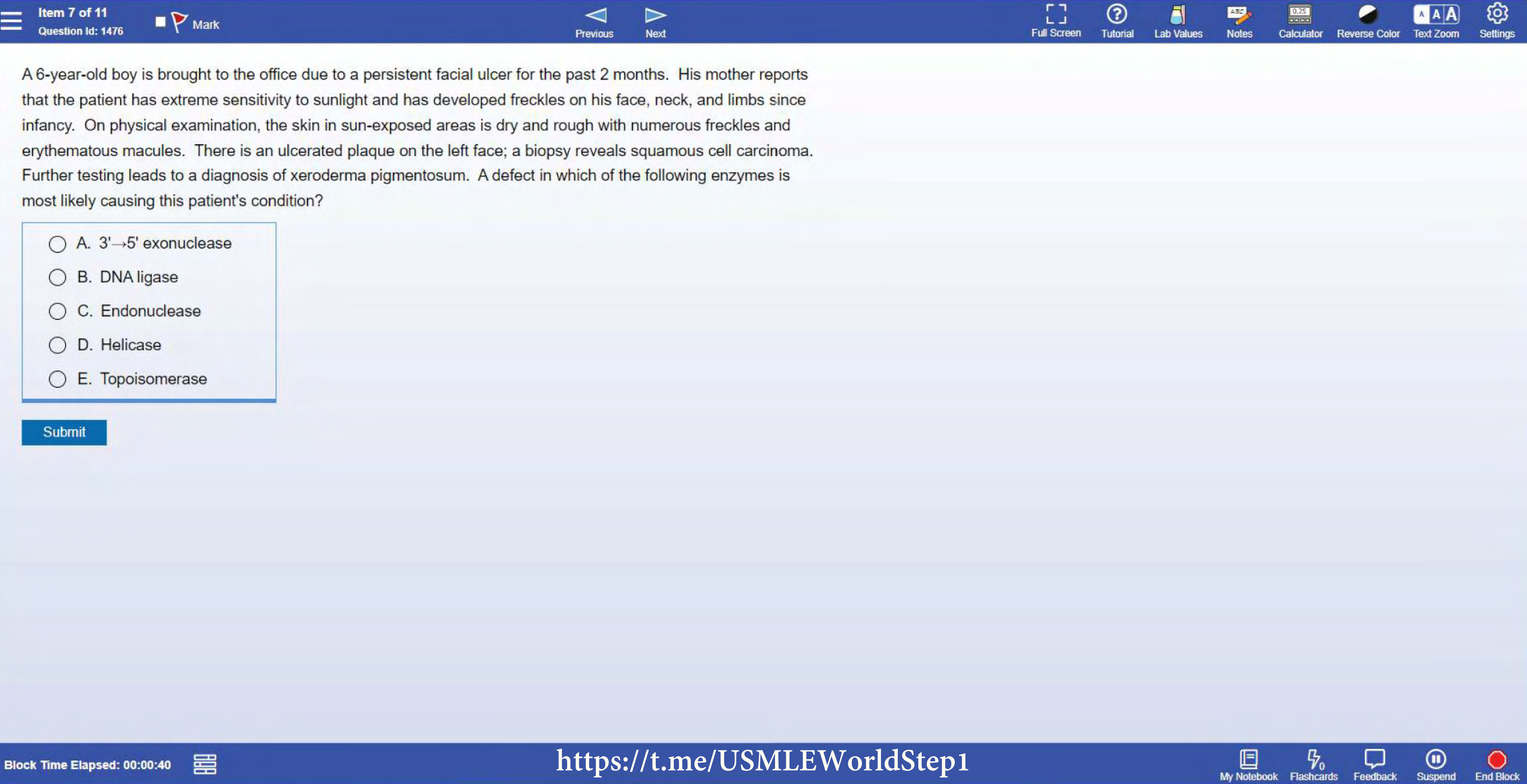
Explanation


Nucleotide excision repair of UV damaged DNA


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 7 of 11
Question Id: 1476

A 6-year-old boy is brought to the office due to a persistent facial ulcer for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

- ○ A. 3'→5' exonuclease
- ○ B. DNA ligase
- ○ C. Endonuclease
- ○ D. Helicase
- ○ E. Topoisomerase

Block Time Elapsed: 00:00:40

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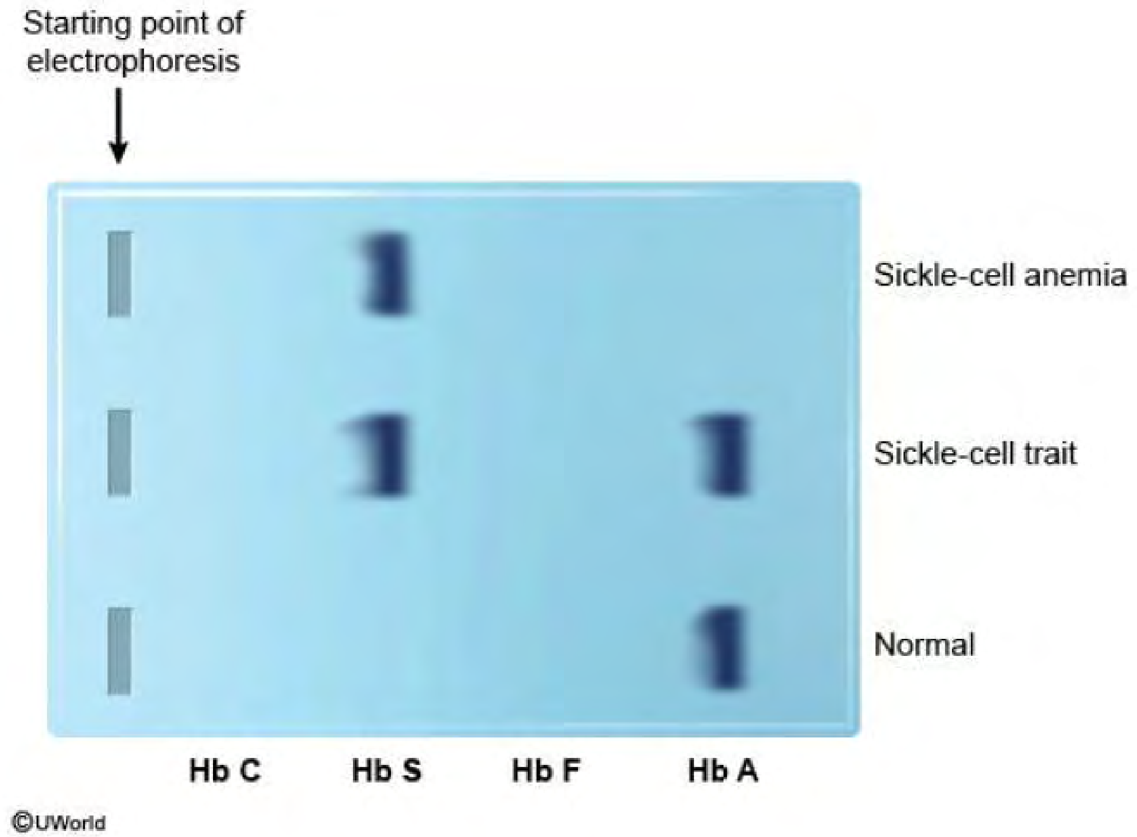
Starting point of electrophoresis
Sickle-cell anemia
Sickle-cell trait
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Hb S
Hb F
Hb A
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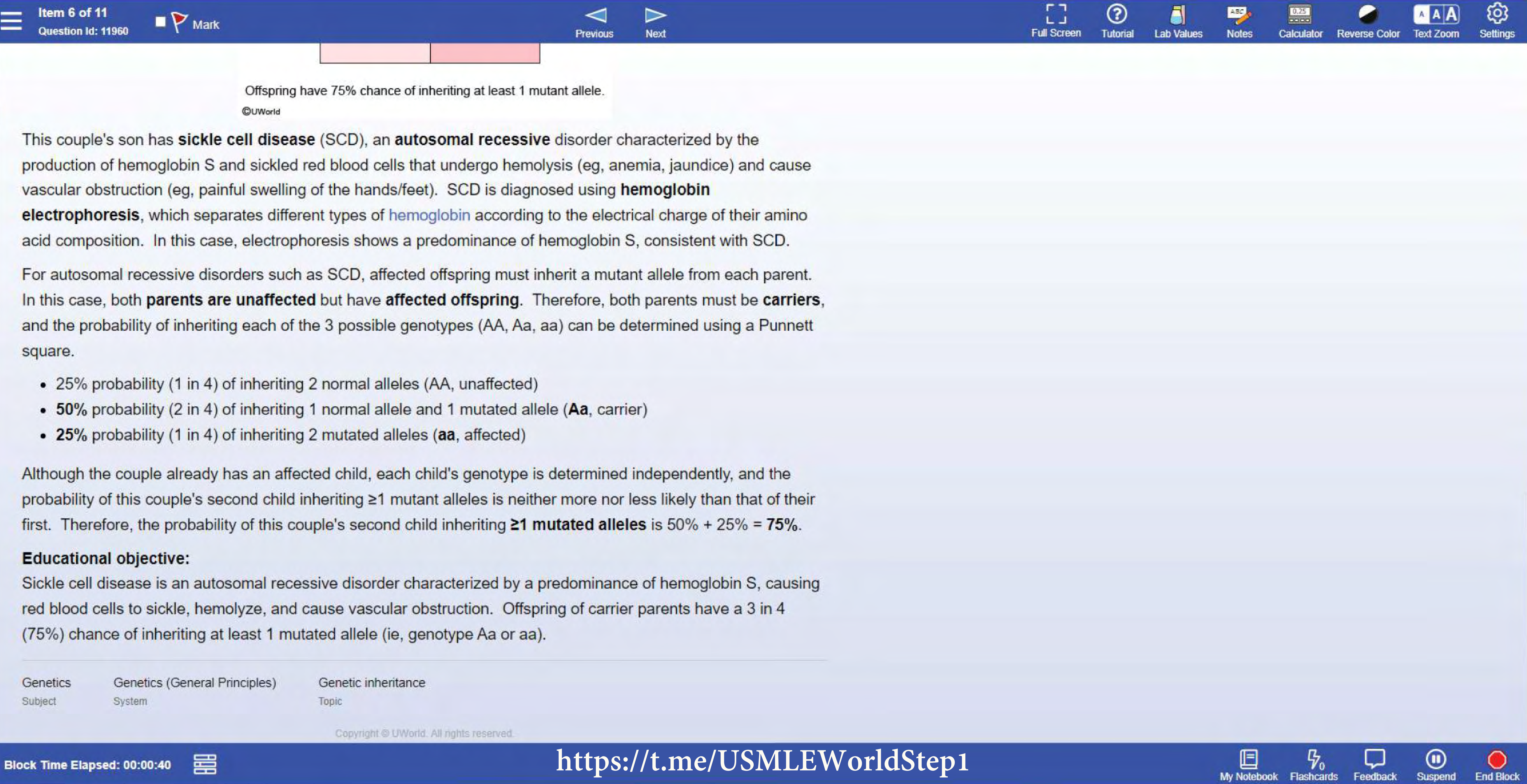

Offspring have 75% chance of inheriting at least 1 mutant allele.

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This couple's son has **sickle cell disease** (SCD), an **autosomal recessive** disorder characterized by the production of hemoglobin S and sickled red blood cells that undergo hemolysis (eg, anemia, jaundice) and cause vascular obstruction (eg, painful swelling of the hands/feet). SCD is diagnosed using **hemoglobin electrophoresis**, which separates different types of hemoglobin according to the electrical charge of their amino acid composition. In this case, electrophoresis shows a predominance of hemoglobin S, consistent with SCD.

For autosomal recessive disorders such as SCD, affected offspring must inherit a mutant allele from each parent. In this case, both **parents are unaffected** but have **affected offspring**. Therefore, both parents must be **carriers**, and the probability of inheriting each of the 3 possible genotypes (AA, Aa, aa) can be determined using a Punnett square.

- 25% probability (1 in 4) of inheriting 2 normal alleles (AA, unaffected)
- **50%** probability (2 in 4) of inheriting 1 normal allele and 1 mutated allele (**Aa**, carrier)
- **25%** probability (1 in 4) of inheriting 2 mutated alleles (**aa**, affected)

Although the couple already has an affected child, each child's genotype is determined independently, and the probability of this couple's second child inheriting ≥1 mutant alleles is neither more nor less likely than that of their first. Therefore, the probability of this couple's second child inheriting **≥1 mutated alleles** is 50% + 25% = **75%**.

Educational objective:

Sickle cell disease is an autosomal recessive disorder characterized by a predominance of hemoglobin S, causing red blood cells to sickle, hemolyze, and cause vascular obstruction. Offspring of carrier parents have a 3 in 4 (75%) chance of inheriting at least 1 mutated allele (ie, genotype Aa or aa).

Genetics	Genetics (General Principles)	Genetic inheritance
Subject	System	Topic

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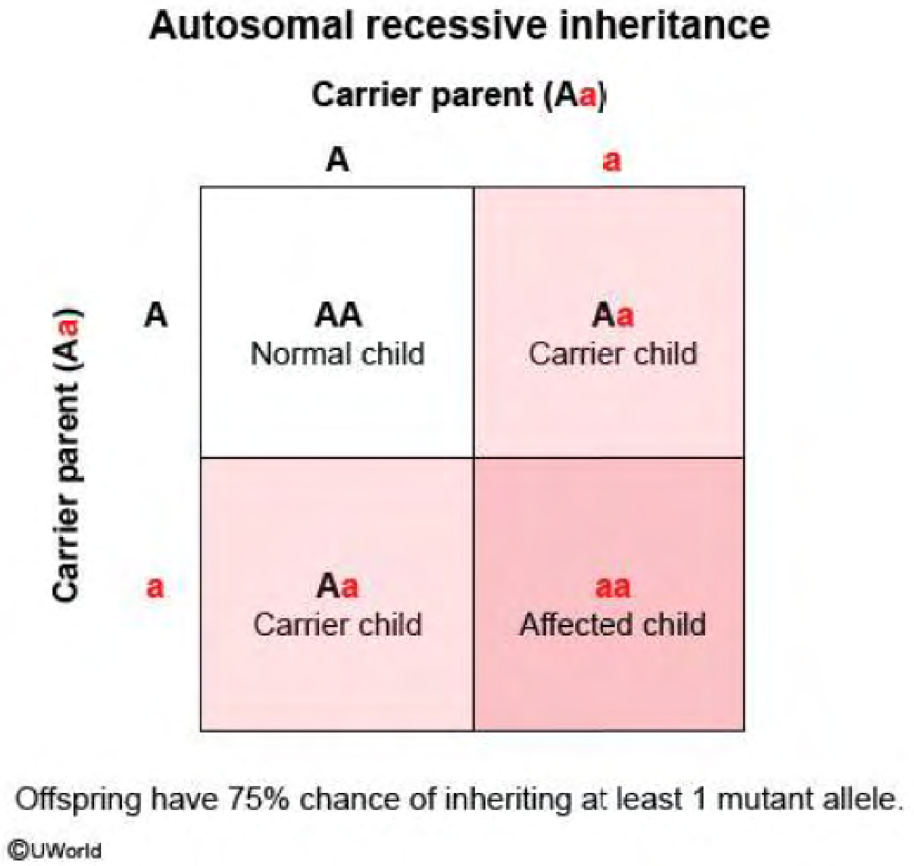

Autosomal recessive inheritance

	Carrier parent (Aa) A	Carrier parent (Aa) a
Carrier parent (Aa) A	AA Normal child	Aa Carrier child
Carrier parent (Aa) a	Aa Carrier child	aa Affected child

Offspring have 75% chance of inheriting at least 1 mutant allele.

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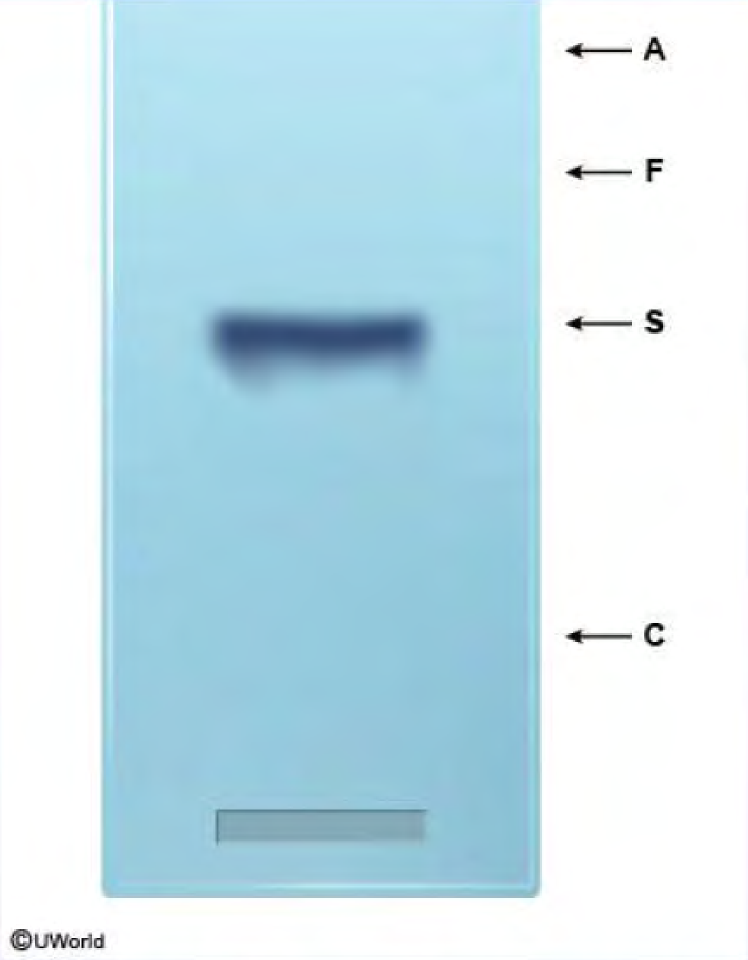
- **50%** probability (2 in 4) of inheriting 1 normal allele and 1 mutated allele (**Aa**, carrier)



The parents are considering having another child. What is the probability they will conceive a child who inherits ≥1 mutated alleles?

○ A. Near 0%
○ B. 25%
✗ ● C. 50%
✓ ○ D. 75%
○ E. 100%

Incorrect
Correct answer
D

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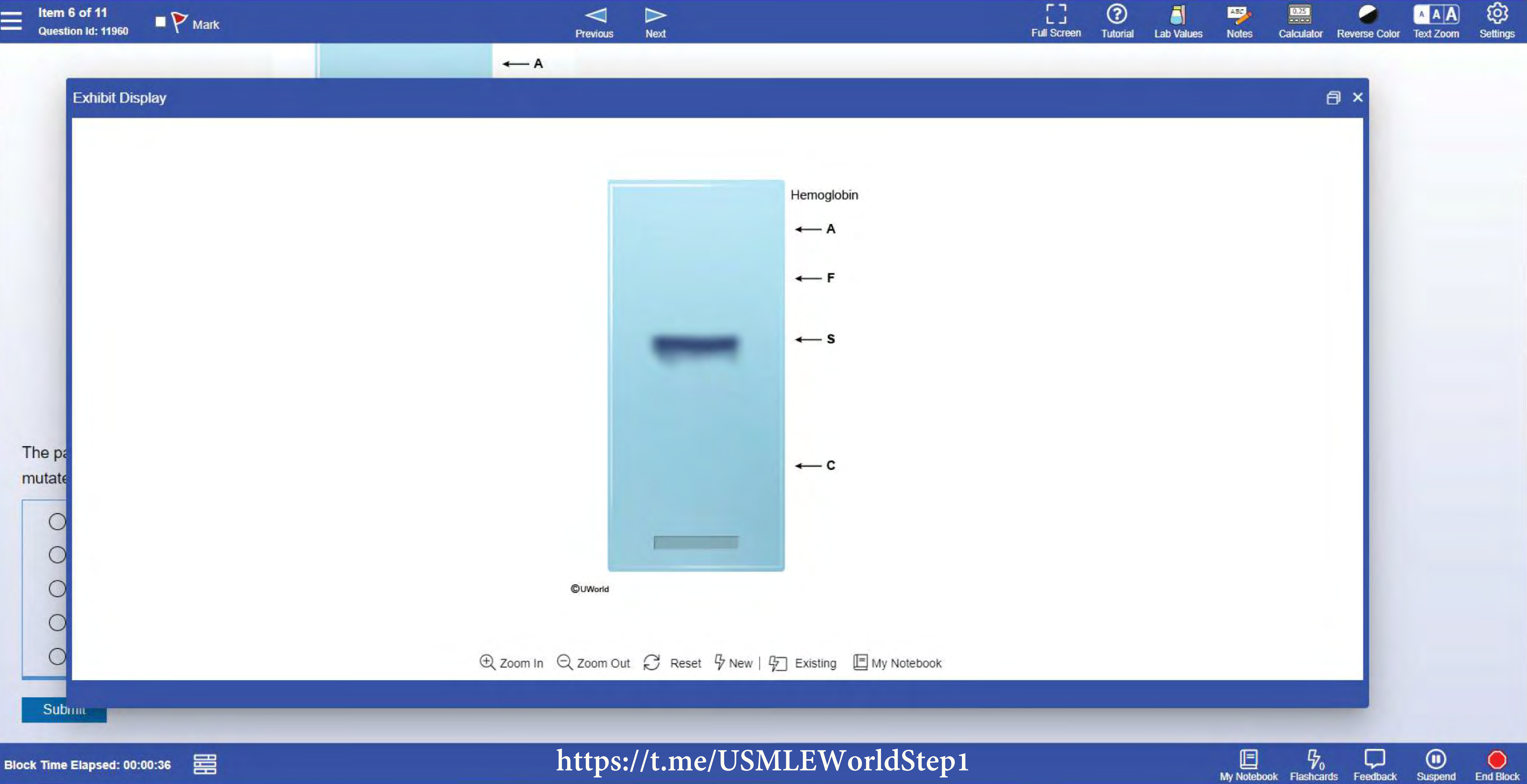
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 6 of 11

Question Id: 11960

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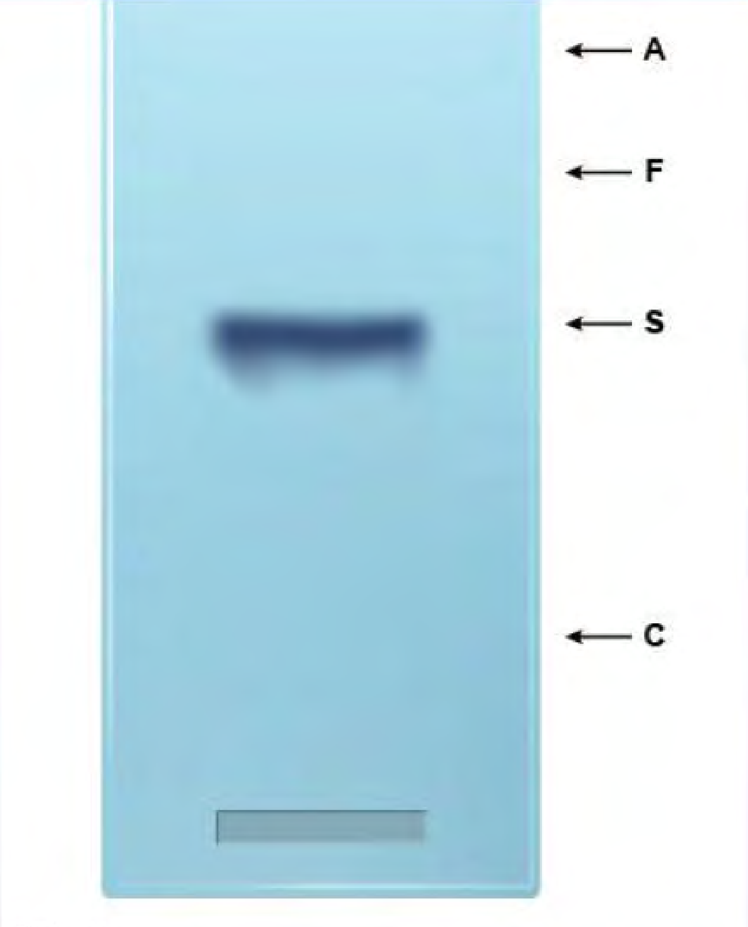

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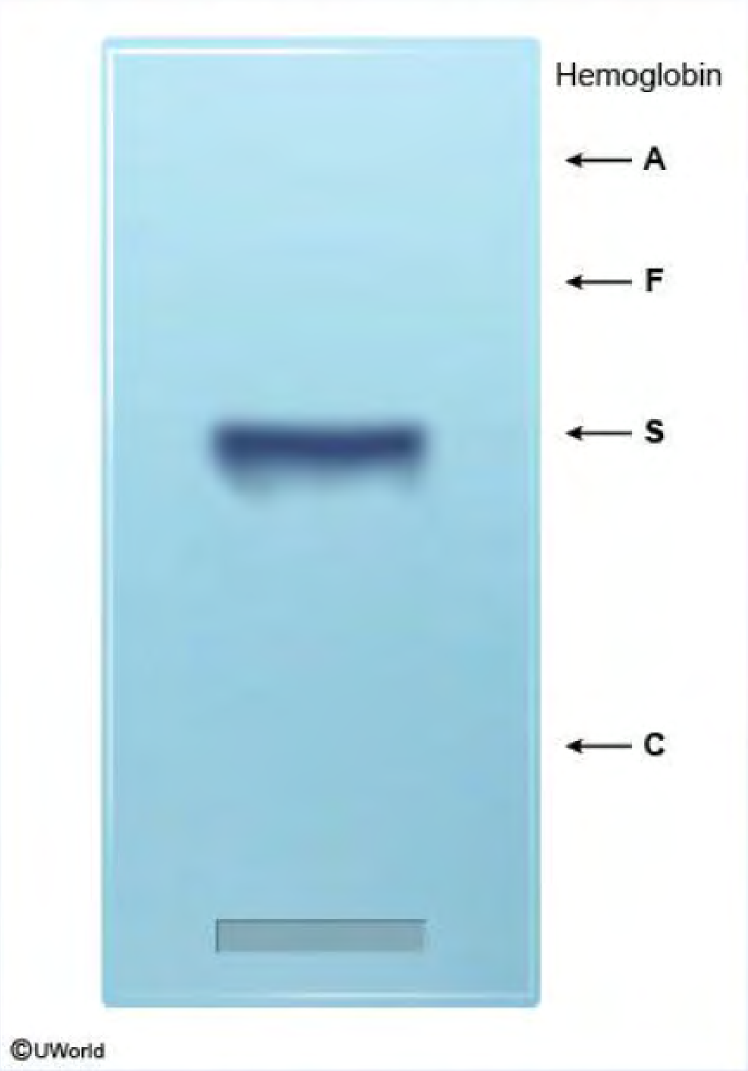
○ A. Near 0%
○ B. 25%
○ C. 50%
○ D. 75%
○ E. 100%

Submit

A 26-year-old woman comes to the office with her husband for genetic counseling. Both of them are healthy with no chronic medical conditions, but their firstborn son has had recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. Hemoglobin electrophoresis is performed on the son at alkaline pH to determine the predominant hemoglobin variants present in his red blood cells. The results are shown below.



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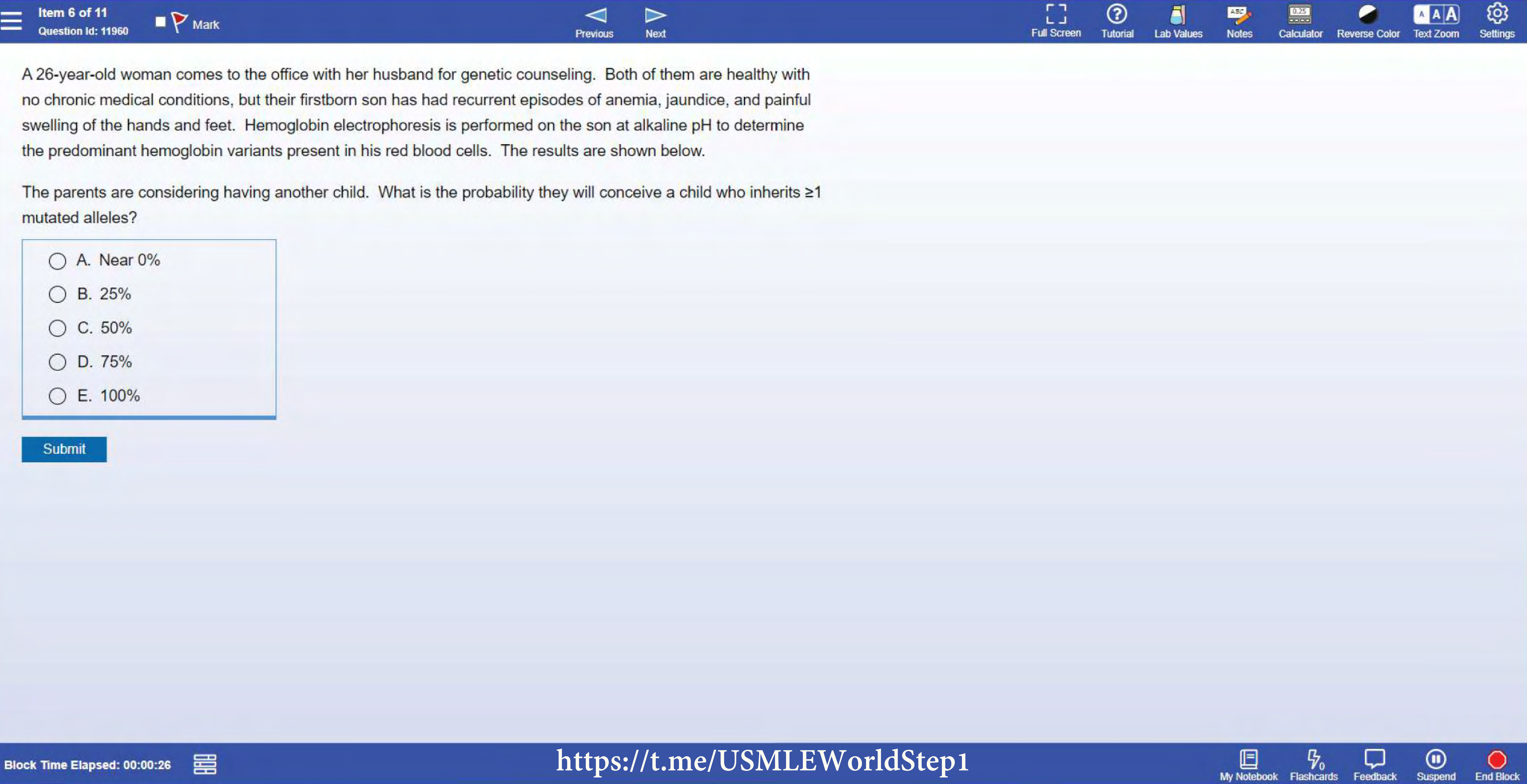
The parents are considering having another child. What is the probability they will conceive a child who inherits ≥1 mutated alleles?

○ A. Near 0%

○ B. 25%


Item 6 of 11
Question Id: 11960
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 26-year-old woman comes to the office with her husband for genetic counseling. Both of them are healthy with no chronic medical conditions, but their firstborn son has had recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. Hemoglobin electrophoresis is performed on the son at alkaline pH to determine the predominant hemoglobin variants present in his red blood cells. The results are shown below.

The parents are considering having another child. What is the probability they will conceive a child who inherits ≥1 mutated alleles?

○ A. Near 0%

○ B. 25%

○ C. 50%

○ D. 75%

○ E. 100%

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Block Time Elapsed: 00:00:26
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 5 of 11
Question Id: 995
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation occurs when GDP is exchanged for GTP on the alpha subunit. Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and activates either adenylate cyclase or phospholipase C, depending on the ligand.

When phenylephrine binds to an alpha-1 receptor on vascular smooth muscle cells, the alpha subunit of the G protein (G_q) **activates phospholipase C**, which breaks down phosphatidylinositol bisphosphate into inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG stimulates protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

(Choice A) Activation of adenylate cyclase leads to the formation of cAMP and subsequent activation of protein kinase A. Protein kinase A phosphorylates intracellular proteins to produce its effects.

(Choice B) Lipoxygenase is an enzyme responsible for the formation of leukotrienes from arachidonic acid. It is not directly involved in the phosphatidylinositol second messenger system.

(Choice C) Phosphodiesterase is an enzyme that terminates the effects of ligands that act via cAMP or cGMP second messenger systems. It has no direct effect on the phosphatidylinositol second messenger system.

(Choice D) The activity of phospholipase C would be unchanged if IP_3 were blocked because phospholipase C exerts its effect before IP_3 in the phosphatidylinositol second messenger system.

Educational objective:

After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated by DAG and calcium; the latter is released from the endoplasmic reticulum under the influence of IP_3.

References

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IP_3 = inositol 1,4,5-trisphosphate; PIP_2 = phosphatidylinositol 4,5-bisphosphate. ©UWorld

G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain coupled with a G protein. In their inactivated state, G proteins exist as heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation occurs when GDP is exchanged for GTP on the alpha subunit. Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and activates either adenylate cyclase or phospholipase C, depending on the ligand.

When phenylephrine binds to an alpha-1 receptor on vascular smooth muscle cells, the alpha subunit of the G protein (G_q) **activates phospholipase C**, which breaks down phosphatidylinositol bisphosphate into inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG stimulates protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

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Educational objective:

After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated

Explanation

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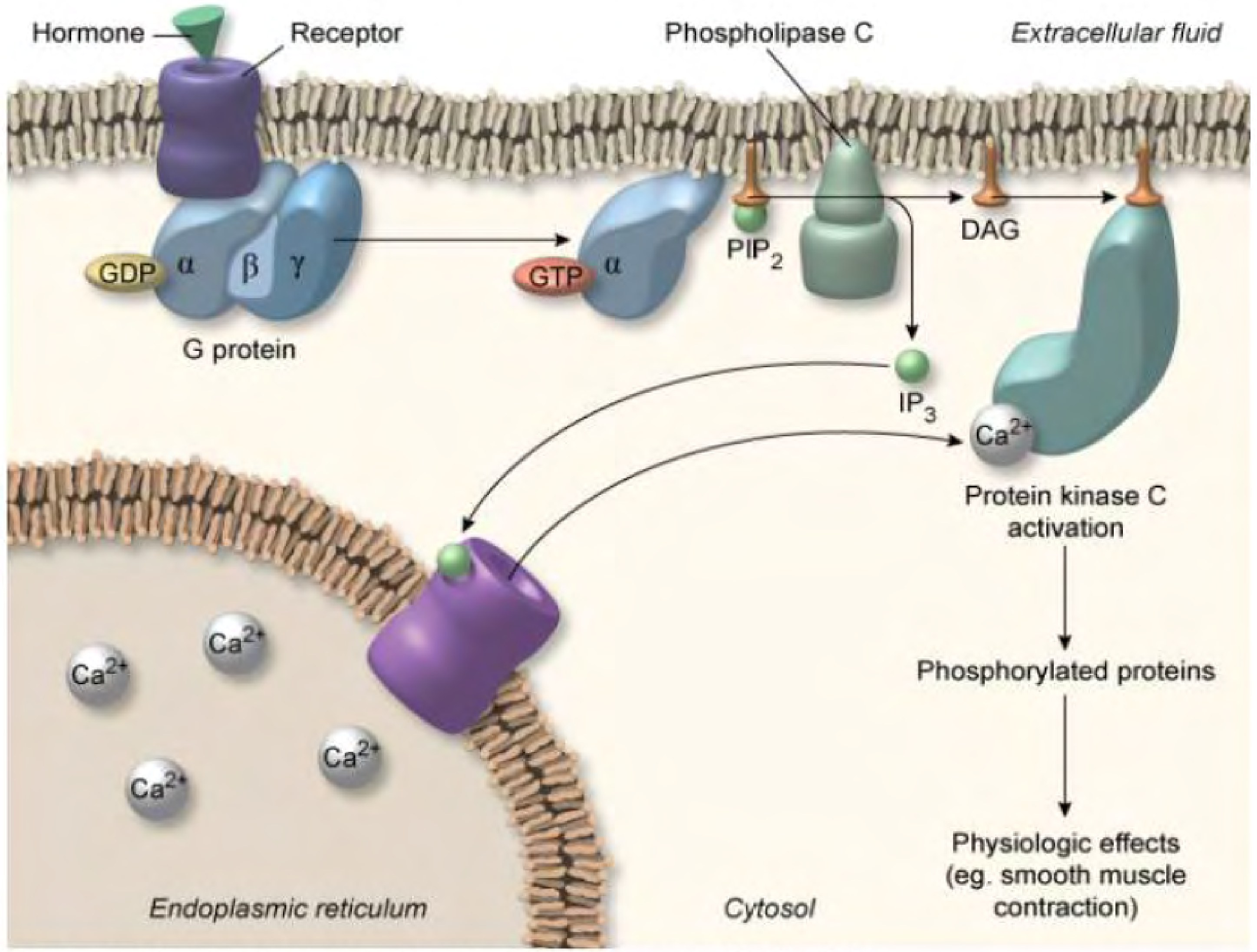
Phosphatidylinositol 2nd messenger system


Hormone
Receptor
Phospholipase C
Extracellular fluid
GDP
α
β
γ
G protein
GTP
α
PIP$_2$
DAG
IP$_3$
Ca^{2+}
Protein kinase C activation
Phosphorylated proteins
Physiologic effects (eg. smooth muscle contraction)
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Endoplasmic reticulum
Cytosol

DAG = diacylglycerol; **GDP** = guanosine 5′-diphosphate; **GTP** = guanosine 5′-triphosphate; **IP$_3$** = inositol 1,4,5-trisphosphate; **PIP$_2$** = phosphatidylinositol 4,5-bisphosphate.

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G prot

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heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation

A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

- ✗ ● A. Adenylate cyclase (9%)
- ○ B. Lipoxygenase (0%)
- ○ C. Phosphodiesterase (4%)
- ○ D. Phospholipase C (36%)
- ✓ ○ E. Protein kinase C (49%)

Incorrect
Correct answer
E

49%
Answered correctly

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2023
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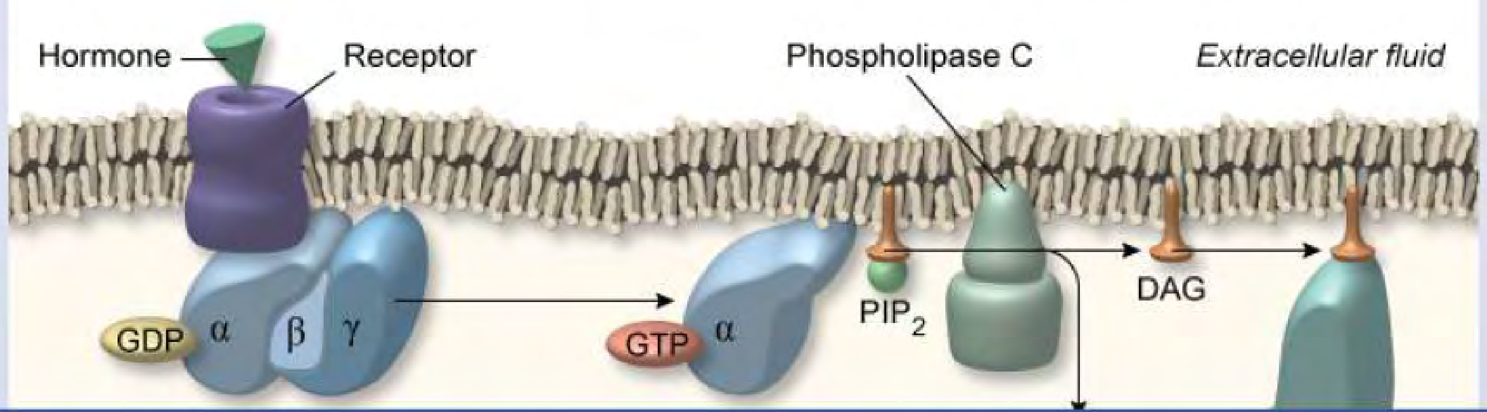
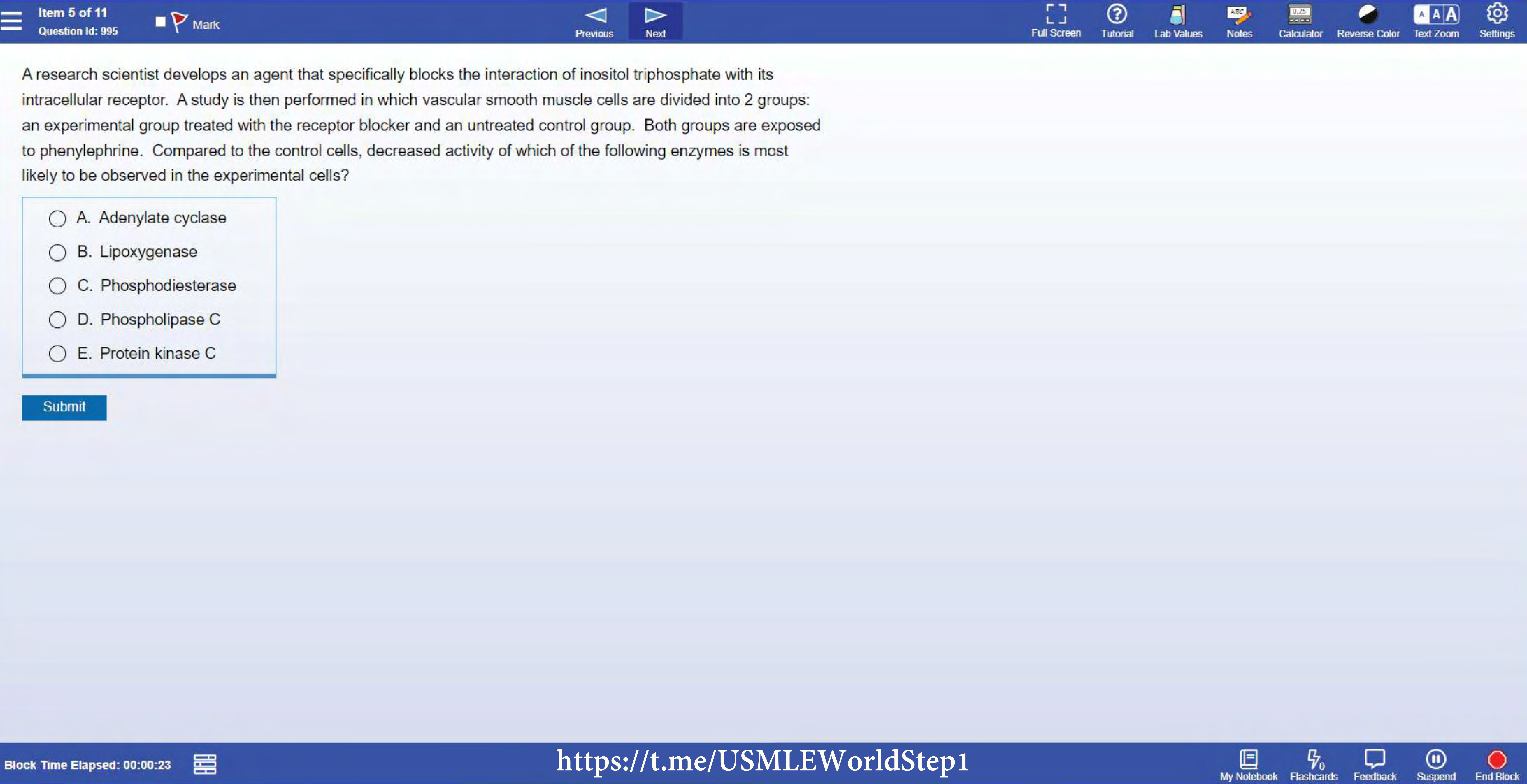
Explanation

Phosphatidylinositol 2nd messenger system




Item 5 of 11
Question Id: 995
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

- ○ A. Adenylate cyclase
- ○ B. Lipoxygenase
- ○ C. Phosphodiesterase
- ○ D. Phospholipase C
- ○ E. Protein kinase C

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My Notebook
Flashcards
Feedback
Suspend
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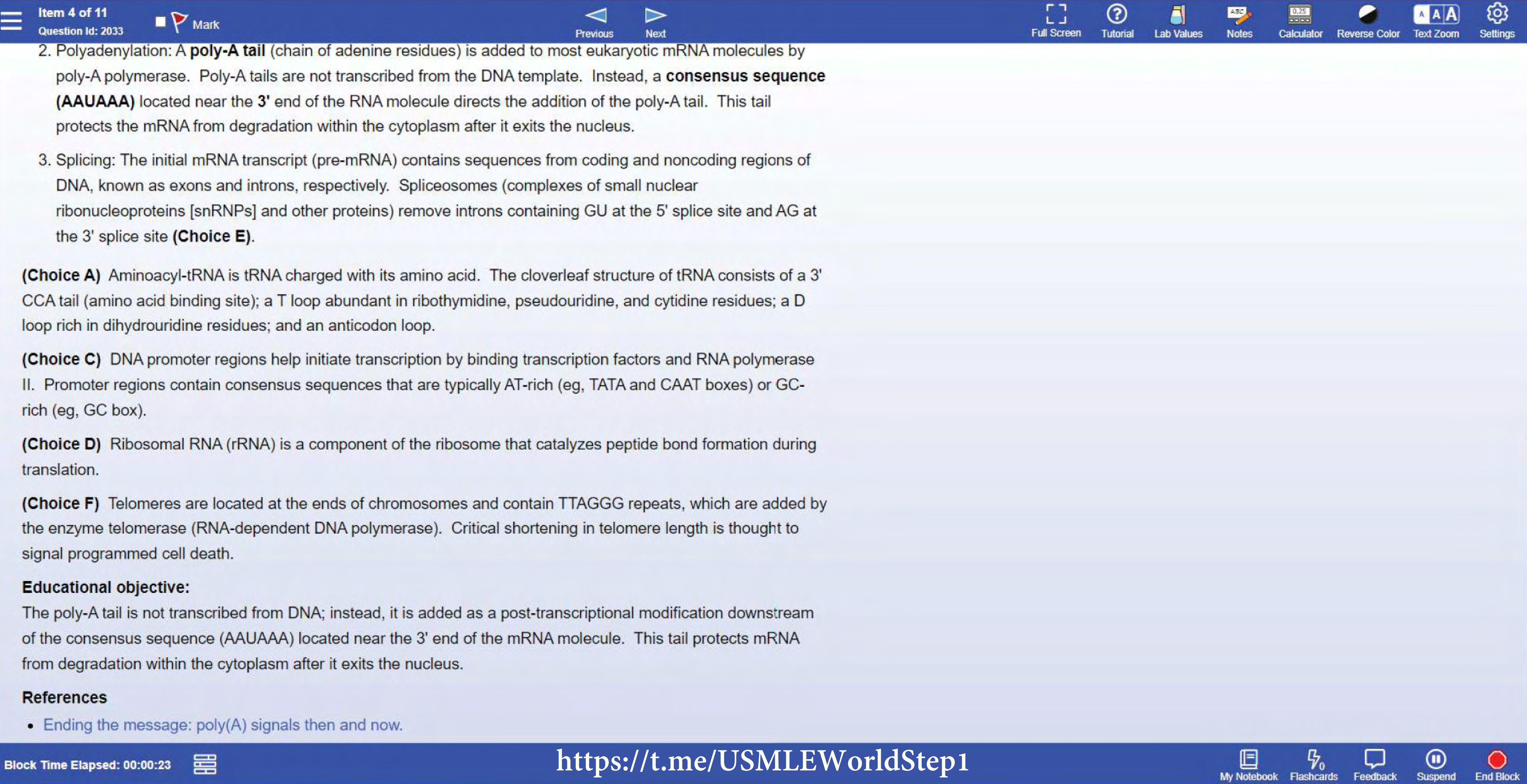


2. Polyadenylation: A **poly-A tail** (chain of adenine residues) is added to most eukaryotic mRNA molecules by poly-A polymerase. Poly-A tails are not transcribed from the DNA template. Instead, a **consensus sequence (AAUAAA)** located near the **3'** end of the RNA molecule directs the addition of the poly-A tail. This tail protects the mRNA from degradation within the cytoplasm after it exits the nucleus.

3. Splicing: The initial mRNA transcript (pre-mRNA) contains sequences from coding and noncoding regions of DNA, known as exons and introns, respectively. Spliceosomes (complexes of small nuclear ribonucleoproteins [snRNPs] and other proteins) remove introns containing GU at the 5' splice site and AG at the 3' splice site **(Choice E)**.

(Choice A) Aminoacyl-tRNA is tRNA charged with its amino acid. The cloverleaf structure of tRNA consists of a 3' CCA tail (amino acid binding site); a T loop abundant in ribothymidine, pseudouridine, and cytidine residues; a D loop rich in dihydrouridine residues; and an anticodon loop.

(Choice C) DNA promoter regions help initiate transcription by binding transcription factors and RNA polymerase II. Promoter regions contain consensus sequences that are typically AT-rich (eg, TATA and CAAT boxes) or GC-rich (eg, GC box).

(Choice D) Ribosomal RNA (rRNA) is a component of the ribosome that catalyzes peptide bond formation during translation.

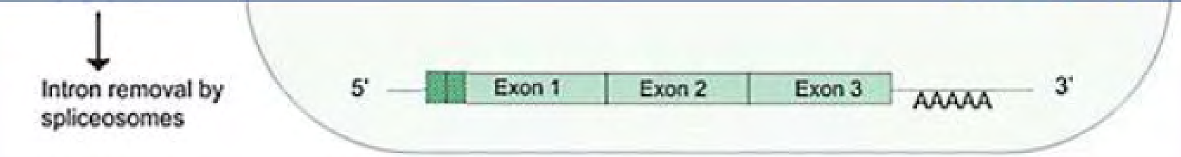
(Choice F) Telomeres are located at the ends of chromosomes and contain TTAGGG repeats, which are added by the enzyme telomerase (RNA-dependent DNA polymerase). Critical shortening in telomere length is thought to signal programmed cell death.

Educational objective:

The poly-A tail is not transcribed from DNA; instead, it is added as a post-transcriptional modification downstream of the consensus sequence (AAUAAA) located near the 3' end of the mRNA molecule. This tail protects mRNA from degradation within the cytoplasm after it exits the nucleus.

References

- Ending the message: poly(A) signals then and now.



In the experiment described above, the poly-A tail on mature mRNA is most likely to bind the latex beads because the adenine residues in this tail would form complementary base pairs with the repeated deoxythymine residues fixed to the beads.

Mature mRNA refers to mRNA that has been processed and is ready for nuclear export and translation into protein. mRNA processing (**post-transcriptional modification**) involves the following steps:

1. 5' capping: A 7-methyl-guanosine cap is added to the 5' end of the mRNA.
2. Polyadenylation: A **poly-A tail** (chain of adenine residues) is added to most eukaryotic mRNA molecules by poly-A polymerase. Poly-A tails are not transcribed from the DNA template. Instead, a **consensus sequence (AAUAAA)** located near the **3'** end of the RNA molecule directs the addition of the poly-A tail. This tail protects the mRNA from degradation within the cytoplasm after it exits the nucleus.
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(Choice C) DNA promoter regions help initiate transcription by binding transcription factors and RNA polymerase II. Promoter regions contain consensus sequences that are typically AT-rich (eg, TATA and CAAT boxes) or GC-rich (eg, GC box).

(Choice D) Ribosomal RNA (rRNA) is a component of the ribosome that catalyzes peptide bond formation during translation.

Item 4 of 11
Question Id: 2033

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Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are

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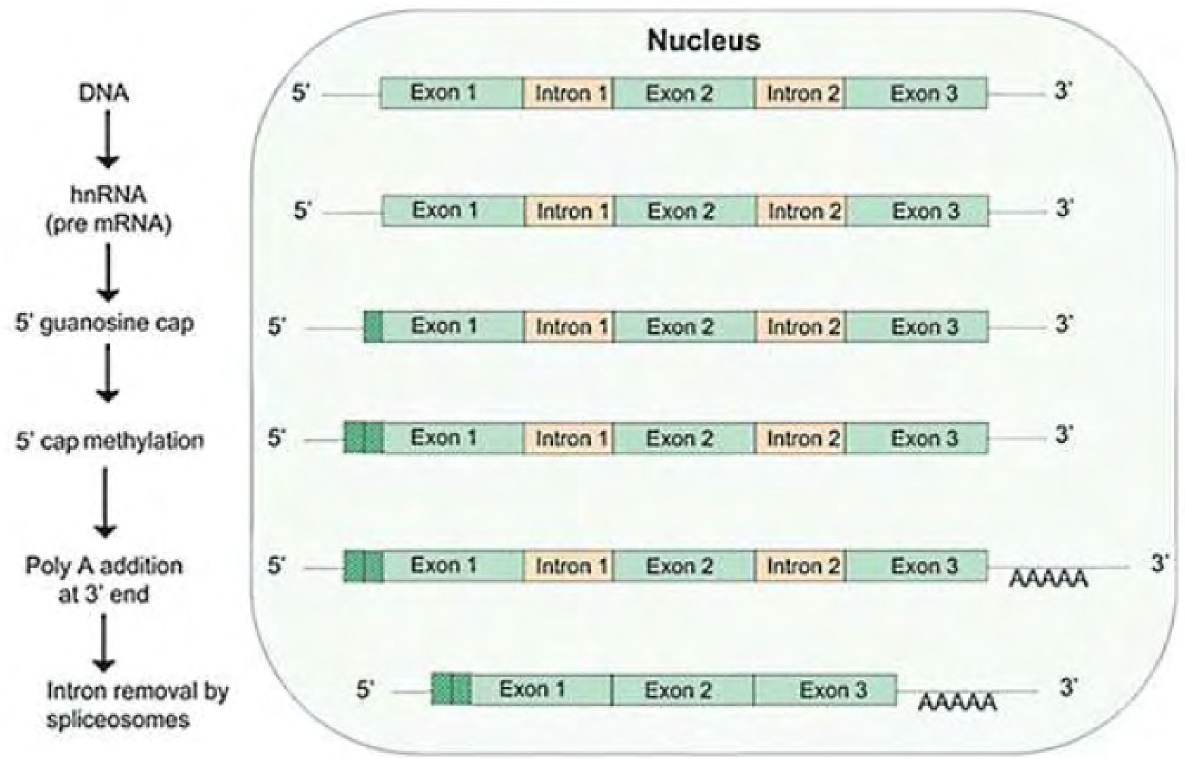

DNA
hnRNA (pre mRNA)
5' guanosine cap
5' cap methylation
Poly A addition at 3' end
Intron removal by spliceosomes
Nucleus
5'
Exon 1
Intron 1
Exon 2
Intron 2
Exon 3
3'
AAAAA

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My Notebook Flashcards Feedback Suspend End Block

In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

- ○ A. Aminoacyl-tRNA (13%)
- ✓ ● B. Mature mRNA (28%)
- ○ C. Promoter regions of DNA (28%)
- ○ D. Ribosomal RNA (7%)
- ○ E. Splice sites of pre-mRNA (5%)
- ○ F. Telomere regions of chromosomes (15%)

Correct

28% Answered correctly

03 secs Time Spent

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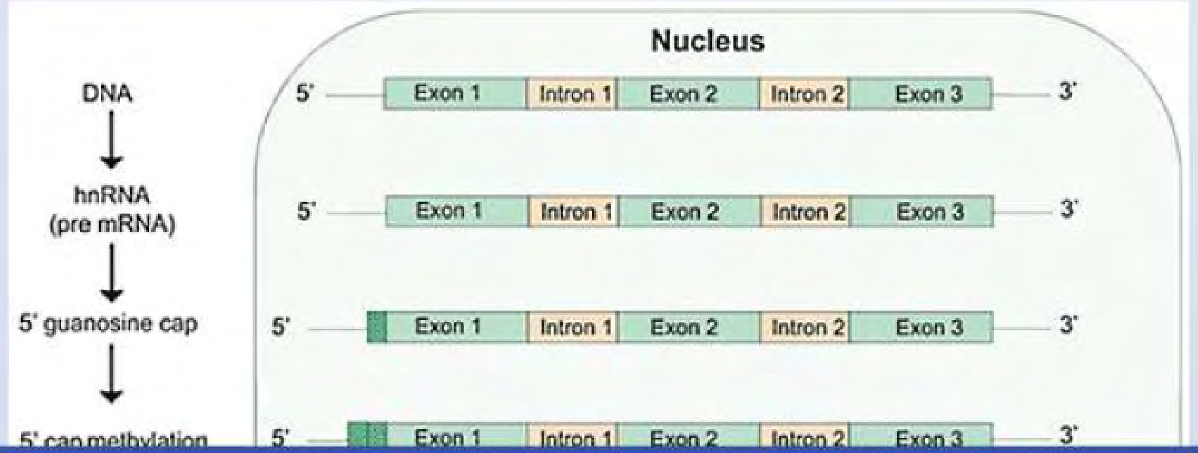
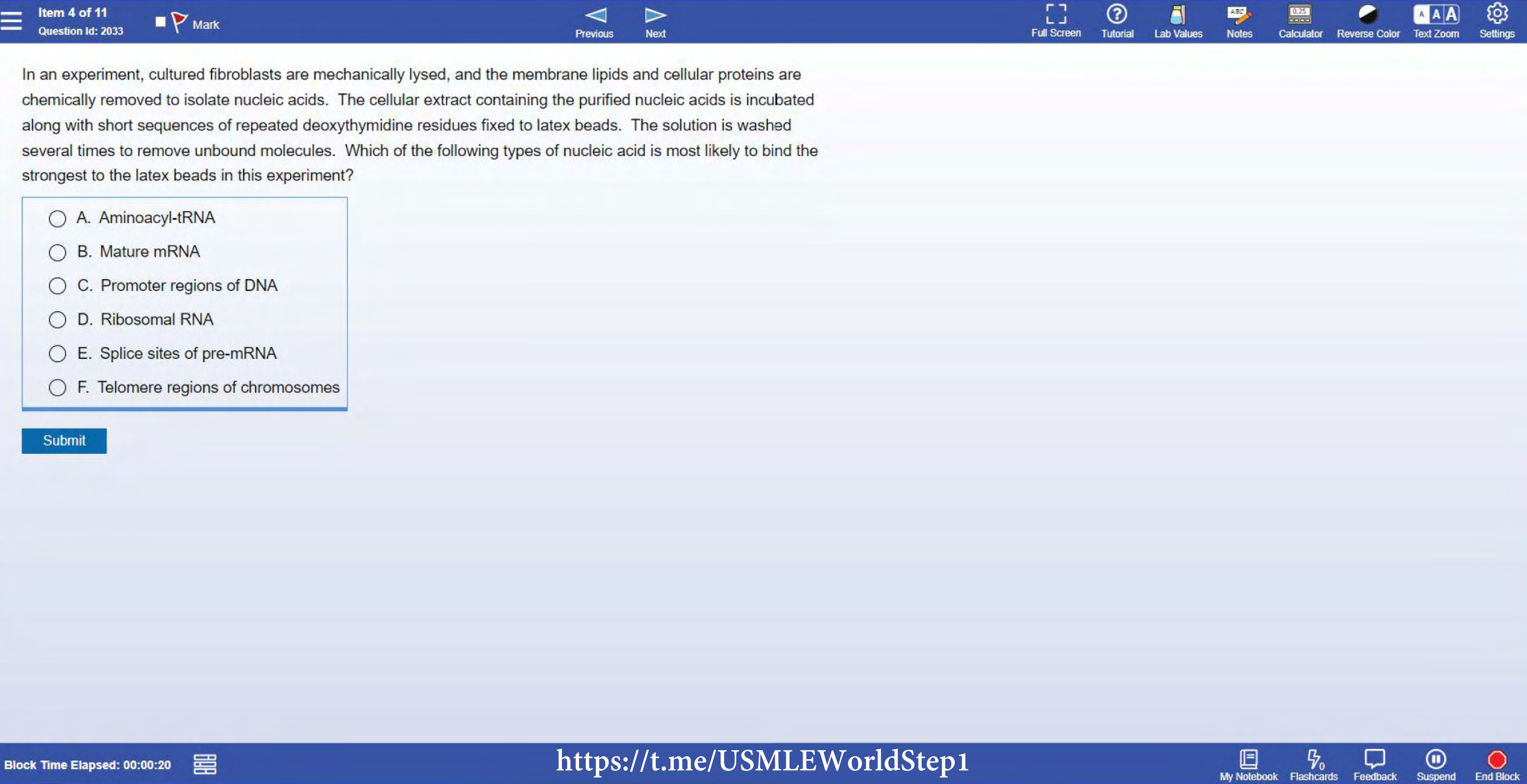
Explanation





Item 4 of 11
Question Id: 2033
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

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○ B. Mature mRNA
○ C. Promoter regions of DNA
○ D. Ribosomal RNA
○ E. Splice sites of pre-mRNA
○ F. Telomere regions of chromosomes

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Flashcards
Feedback
Suspend
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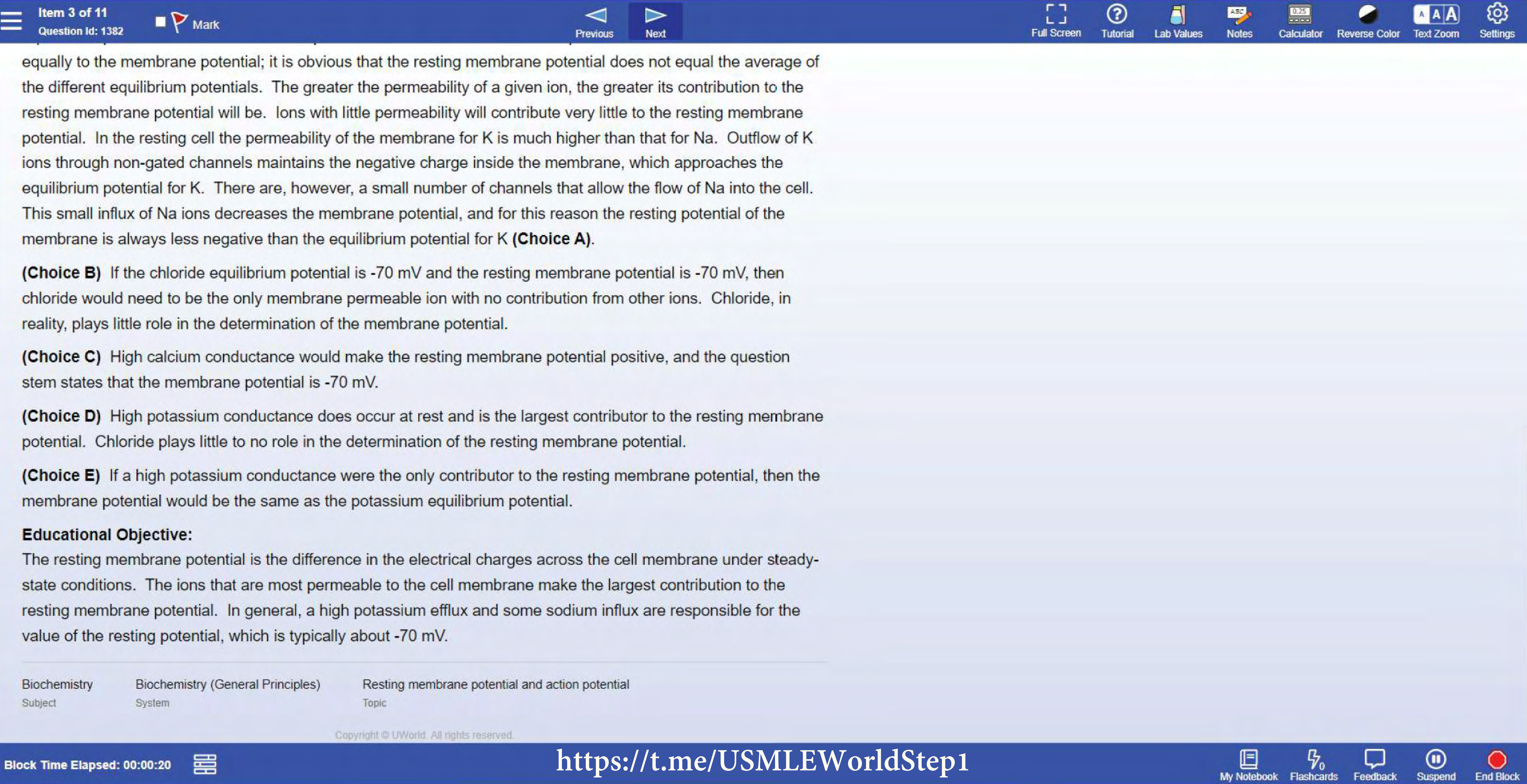

equally to the membrane potential; it is obvious that the resting membrane potential does not equal the average of the different equilibrium potentials. The greater the permeability of a given ion, the greater its contribution to the resting membrane potential will be. Ions with little permeability will contribute very little to the resting membrane potential. In the resting cell the permeability of the membrane for K is much higher than that for Na. Outflow of K ions through non-gated channels maintains the negative charge inside the membrane, which approaches the equilibrium potential for K. There are, however, a small number of channels that allow the flow of Na into the cell. This small influx of Na ions decreases the membrane potential, and for this reason the resting potential of the membrane is always less negative than the equilibrium potential for K **(Choice A)**.

(Choice B) If the chloride equilibrium potential is -70 mV and the resting membrane potential is -70 mV, then chloride would need to be the only membrane permeable ion with no contribution from other ions. Chloride, in reality, plays little role in the determination of the membrane potential.

(Choice C) High calcium conductance would make the resting membrane potential positive, and the question stem states that the membrane potential is -70 mV.

(Choice D) High potassium conductance does occur at rest and is the largest contributor to the resting membrane potential. Chloride plays little to no role in the determination of the resting membrane potential.

(Choice E) If a high potassium conductance were the only contributor to the resting membrane potential, then the membrane potential would be the same as the potassium equilibrium potential.

Educational Objective:

The resting membrane potential is the difference in the electrical charges across the cell membrane under steady-state conditions. The ions that are most permeable to the cell membrane make the largest contribution to the resting membrane potential. In general, a high potassium efflux and some sodium influx are responsible for the value of the resting potential, which is typically about -70 mV.

Biochemistry	Biochemistry (General Principles)	Resting membrane potential and action potential
Subject	System	Topic

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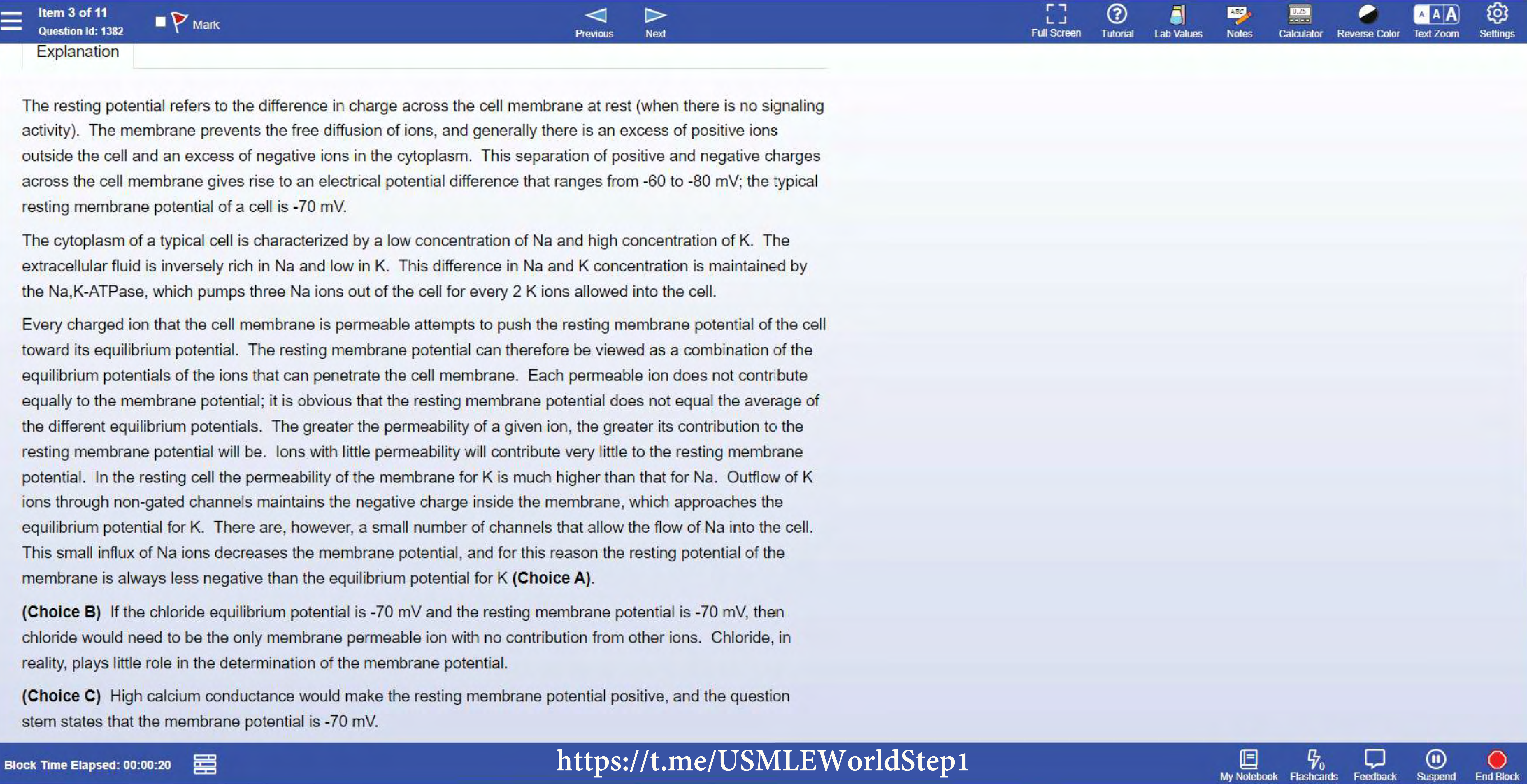


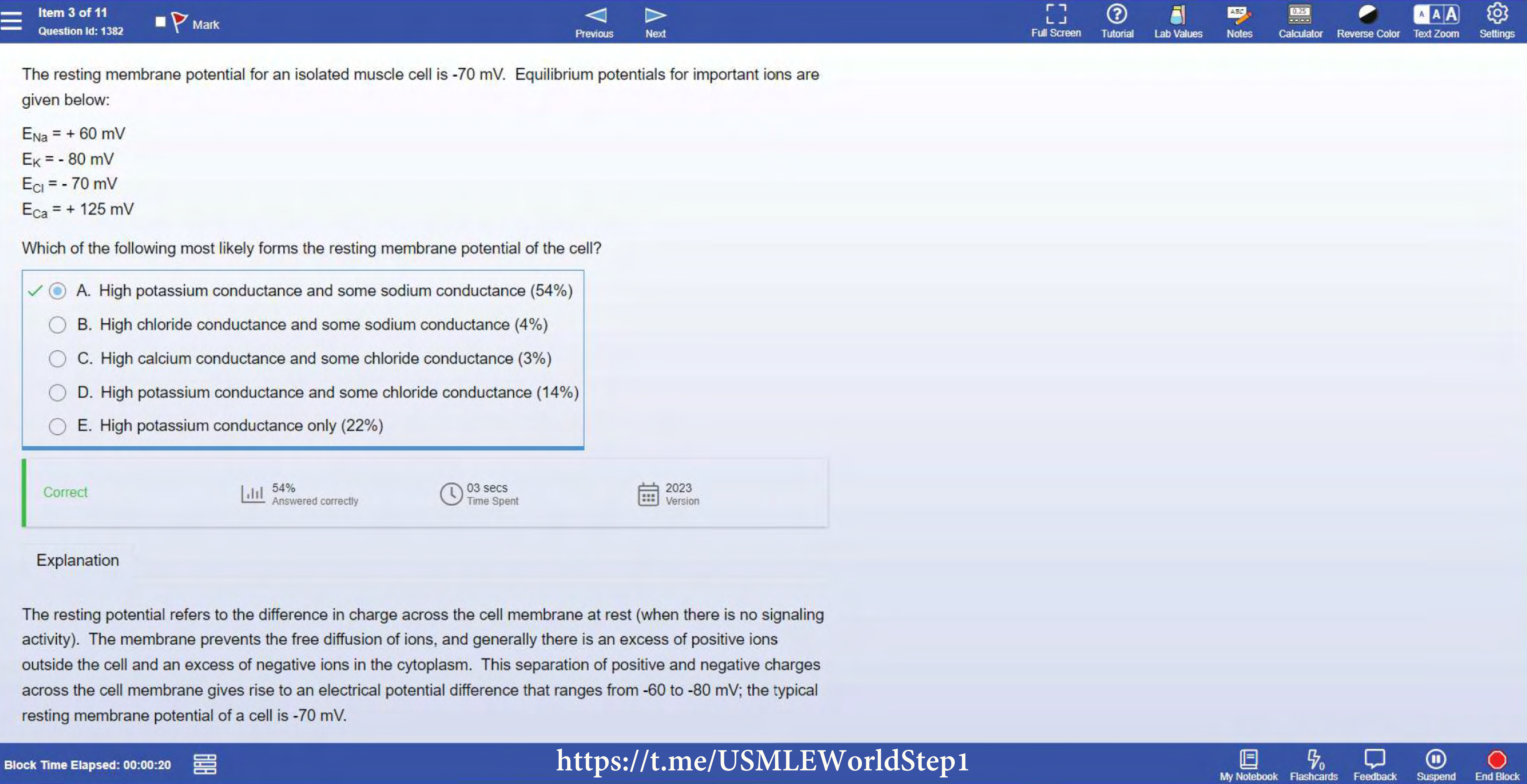
The resting potential refers to the difference in charge across the cell membrane at rest (when there is no signaling activity). The membrane prevents the free diffusion of ions, and generally there is an excess of positive ions outside the cell and an excess of negative ions in the cytoplasm. This separation of positive and negative charges across the cell membrane gives rise to an electrical potential difference that ranges from -60 to -80 mV; the typical resting membrane potential of a cell is -70 mV.

The cytoplasm of a typical cell is characterized by a low concentration of Na and high concentration of K. The extracellular fluid is inversely rich in Na and low in K. This difference in Na and K concentration is maintained by the Na,K-ATPase, which pumps three Na ions out of the cell for every 2 K ions allowed into the cell.

Every charged ion that the cell membrane is permeable attempts to push the resting membrane potential of the cell toward its equilibrium potential. The resting membrane potential can therefore be viewed as a combination of the equilibrium potentials of the ions that can penetrate the cell membrane. Each permeable ion does not contribute equally to the membrane potential; it is obvious that the resting membrane potential does not equal the average of the different equilibrium potentials. The greater the permeability of a given ion, the greater its contribution to the resting membrane potential will be. Ions with little permeability will contribute very little to the resting membrane potential. In the resting cell the permeability of the membrane for K is much higher than that for Na. Outflow of K ions through non-gated channels maintains the negative charge inside the membrane, which approaches the equilibrium potential for K. There are, however, a small number of channels that allow the flow of Na into the cell. This small influx of Na ions decreases the membrane potential, and for this reason the resting potential of the membrane is always less negative than the equilibrium potential for K **(Choice A)**.

(Choice B) If the chloride equilibrium potential is -70 mV and the resting membrane potential is -70 mV, then chloride would need to be the only membrane permeable ion with no contribution from other ions. Chloride, in reality, plays little role in the determination of the membrane potential.

(Choice C) High calcium conductance would make the resting membrane potential positive, and the question stem states that the membrane potential is -70 mV.


Item 3 of 11
Question Id: 1382
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

The resting membrane potential for an isolated muscle cell is -70 mV. Equilibrium potentials for important ions are given below:

E_{Na} = + 60 mV
E_K = - 80 mV
E_{Cl} = - 70 mV
E_{Ca} = + 125 mV

Which of the following most likely forms the resting membrane potential of the cell?

✓ ● A. High potassium conductance and some sodium conductance (54%)
○ B. High chloride conductance and some sodium conductance (4%)
○ C. High calcium conductance and some chloride conductance (3%)
○ D. High potassium conductance and some chloride conductance (14%)
○ E. High potassium conductance only (22%)

Correct | 54% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

The resting potential refers to the difference in charge across the cell membrane at rest (when there is no signaling activity). The membrane prevents the free diffusion of ions, and generally there is an excess of positive ions outside the cell and an excess of negative ions in the cytoplasm. This separation of positive and negative charges across the cell membrane gives rise to an electrical potential difference that ranges from -60 to -80 mV; the typical resting membrane potential of a cell is -70 mV.

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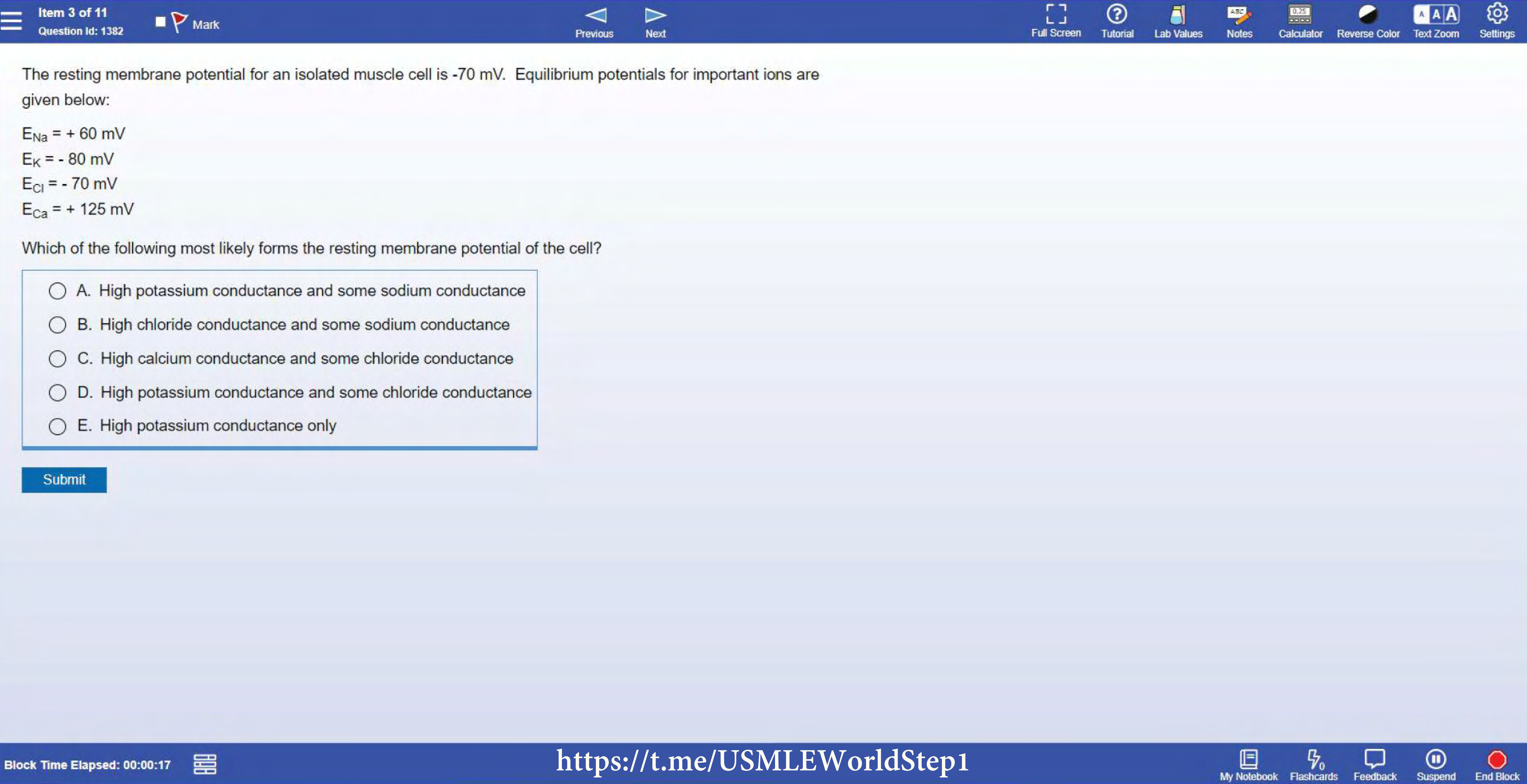
Item 3 of 11
Question Id: 1382
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ B. High chloride conductance and some sodium conductance
- ○ C. High calcium conductance and some chloride conductance
- ○ D. High potassium conductance and some chloride conductance
- ○ E. High potassium conductance only

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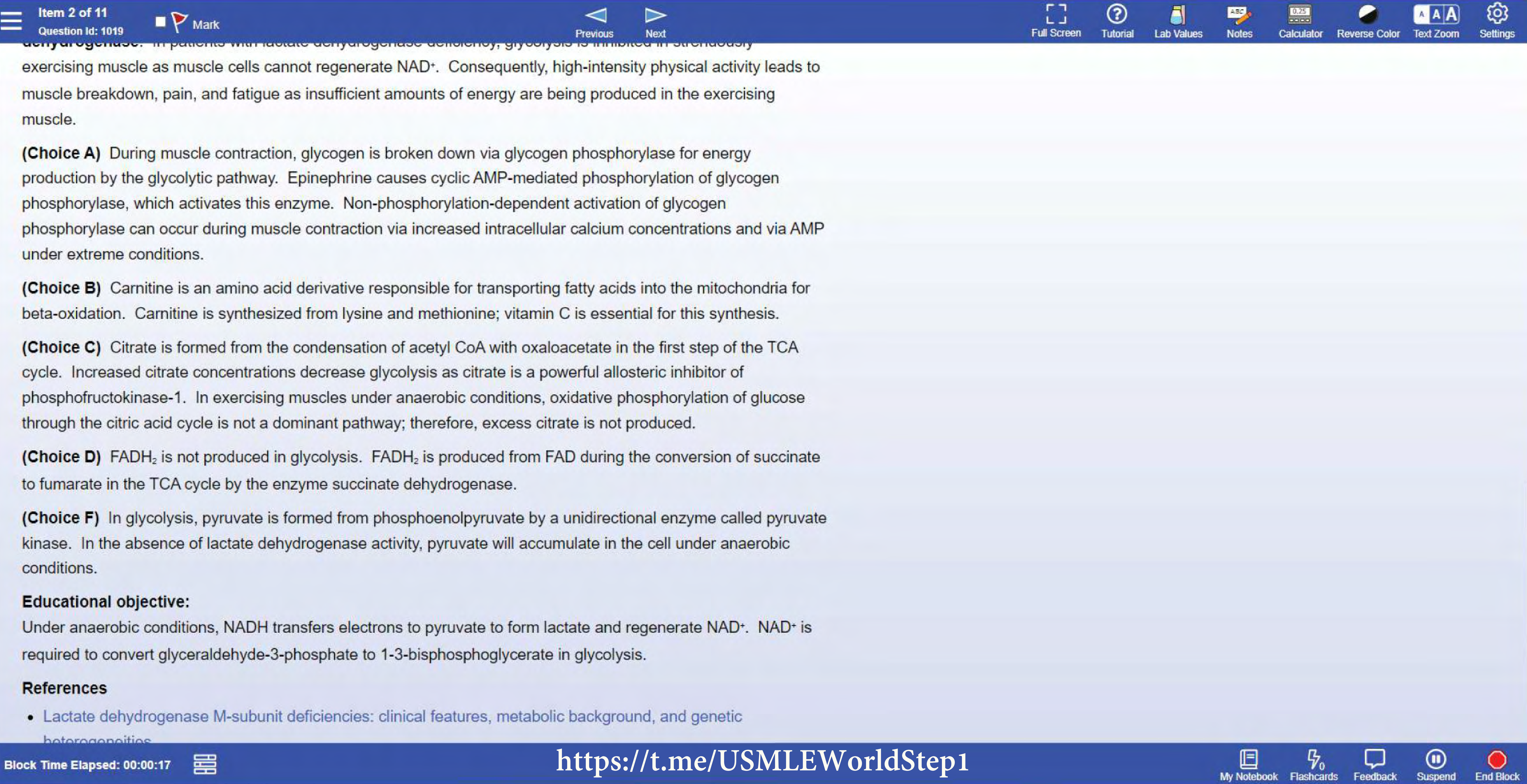

dehydrogenase. In patients with lactate dehydrogenase deficiency, glycolysis is inhibited in strenuously exercising muscle as muscle cells cannot regenerate NAD^+. Consequently, high-intensity physical activity leads to muscle breakdown, pain, and fatigue as insufficient amounts of energy are being produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

(Choice B) Carnitine is an amino acid derivative responsible for transporting fatty acids into the mitochondria for beta-oxidation. Carnitine is synthesized from lysine and methionine; vitamin C is essential for this synthesis.

(Choice C) Citrate is formed from the condensation of acetyl CoA with oxaloacetate in the first step of the TCA cycle. Increased citrate concentrations decrease glycolysis as citrate is a powerful allosteric inhibitor of phosphofructokinase-1. In exercising muscles under anaerobic conditions, oxidative phosphorylation of glucose through the citric acid cycle is not a dominant pathway; therefore, excess citrate is not produced.

(Choice D) $FADH_2$ is not produced in glycolysis. $FADH_2$ is produced from FAD during the conversion of succinate to fumarate in the TCA cycle by the enzyme succinate dehydrogenase.

(Choice F) In glycolysis, pyruvate is formed from phosphoenolpyruvate by a unidirectional enzyme called pyruvate kinase. In the absence of lactate dehydrogenase activity, pyruvate will accumulate in the cell under anaerobic conditions.

Educational objective:

Under anaerobic conditions, NADH transfers electrons to pyruvate to form lactate and regenerate NAD^+. NAD^+ is required to convert glyceraldehyde-3-phosphate to 1-3-bisphosphoglycerate in glycolysis.

References

- Lactate dehydrogenase M-subunit deficiencies: clinical features, metabolic background, and genetic heterogeneities

1,3-BPG = 1,3-bisphosphoglyceric acid.

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In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid (TCA) cycle. When oxygen is depleted (eg, in exercising muscle), pyruvate is converted to lactate (**anaerobic glycolysis**).

During glycolysis, glyceraldehyde-3-phosphate (G3P) is converted to 1-3-bisphosphoglycerate (BPG) by the enzyme G3P dehydrogenase. This enzyme reduces NAD^+ to NADH. NAD^+ is present in limited amounts in most cells, and it must be regenerated from NADH for glycolysis to continue. Under aerobic conditions, NAD^+ is converted to NADH in the TCA cycle. NADH is then reconverted to NAD^+ in the electron transport chain as the energy in NADH is utilized to synthesize ATP.

In anaerobic glycolysis, **NAD+** is **regenerated** from NADH when pyruvate is converted to lactate via **lactate dehydrogenase**. In patients with lactate dehydrogenase deficiency, glycolysis is inhibited in strenuously exercising muscle as muscle cells cannot regenerate NAD^+. Consequently, high-intensity physical activity leads to muscle breakdown, pain, and fatigue as insufficient amounts of energy are being produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

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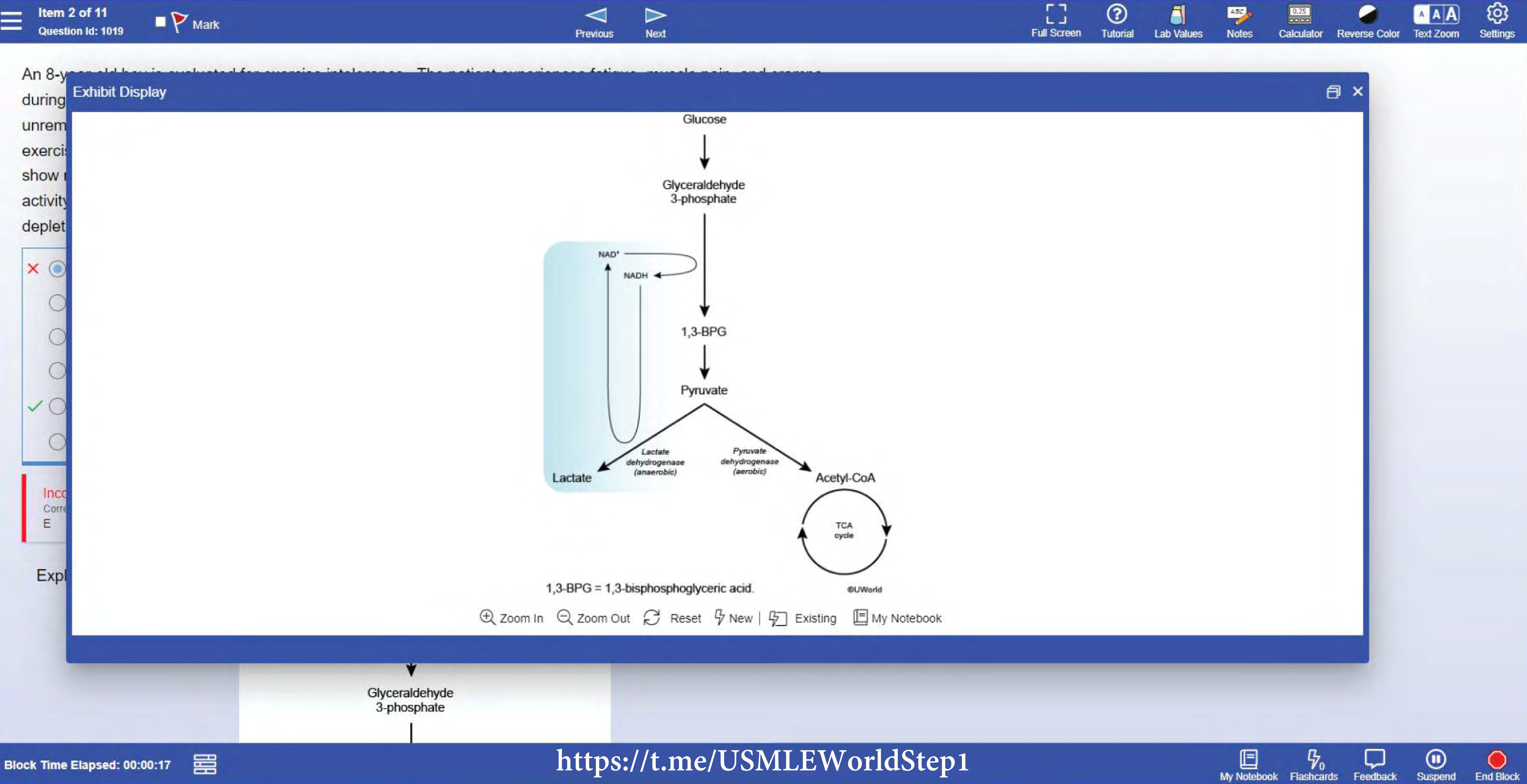
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Glucose
Glyceraldehyde 3-phosphate
NAD⁺
NADH
1,3-BPG
Pyruvate
Lactate dehydrogenase (anaerobic)
Pyruvate dehydrogenase (aerobic)
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Acetyl-CoA
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Zoom In
Zoom Out
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Flashcards
Feedback
Suspend
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Item 2 of 11
Question Id: 1019

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1,3-BPG = 1,3-bisphosphoglyceric acid.

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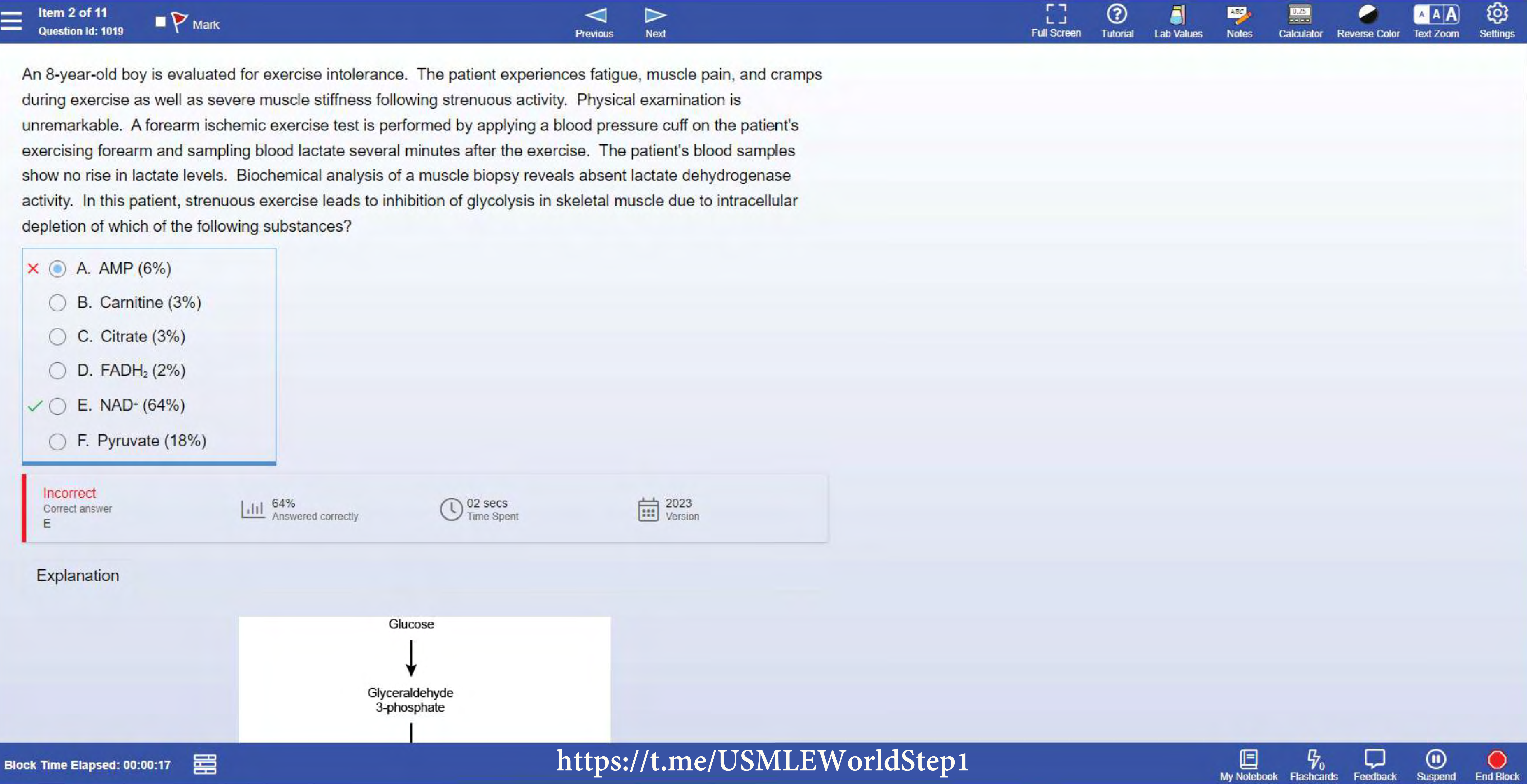
Item 2 of 11
Question Id: 1019
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 8-year-old boy is evaluated for exercise intolerance. The patient experiences fatigue, muscle pain, and cramps during exercise as well as severe muscle stiffness following strenuous activity. Physical examination is unremarkable. A forearm ischemic exercise test is performed by applying a blood pressure cuff on the patient's exercising forearm and sampling blood lactate several minutes after the exercise. The patient's blood samples show no rise in lactate levels. Biochemical analysis of a muscle biopsy reveals absent lactate dehydrogenase activity. In this patient, strenuous exercise leads to inhibition of glycolysis in skeletal muscle due to intracellular depletion of which of the following substances?

- ✗ ● A. AMP (6%)
- ○ B. Carnitine (3%)
- ○ C. Citrate (3%)
- ○ D. $FADH_2$ (2%)
- ✓ ○ E. NAD^+ (64%)
- ○ F. Pyruvate (18%)

Incorrect
Correct answer
E

64%
Answered correctly

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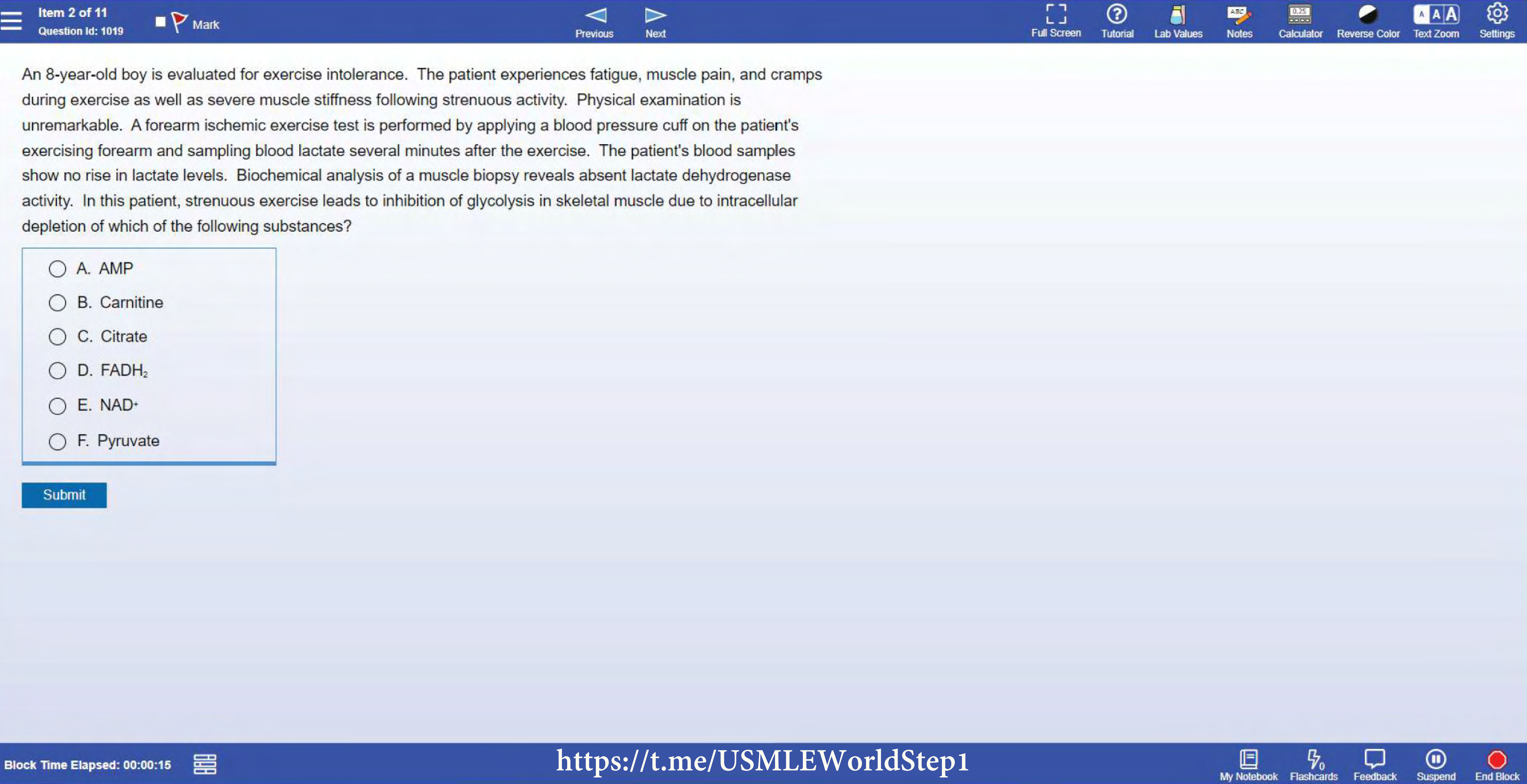
Explanation

Glucose
Glyceraldehyde 3-phosphate

Block Time Elapsed: 00:00:17
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 2 of 11
Question Id: 1019
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ B. Carnitine
○ C. Citrate
○ D. $FADH_2$
○ E. NAD^+
○ F. Pyruvate

Submit
Block Time Elapsed: 00:00:15

My Notebook
Flashcards
Feedback
Suspend
End Block

Item 1 of 11
Question Id: 1475
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Block Time Elapsed: 00:00:15
My Notebook
Flashcards
Feedback
Suspend
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AP = apurinic/apyrimidinic.

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Excessive consumption of dietary **nitrites** can promote the **deamination of cytosine**, adenine, and guanine to form uracil, hypoxanthine, and xanthine, respectively. If these abnormal bases are not removed and replaced with the correct base, persistent DNA mutations and **carcinogenesis** may result.

Base excision repair (not to be confused with nucleotide excision or mismatch repair) is responsible for fixing various **non-bulky** (ie, does not substantially disrupt DNA helix shape) base alterations such as depurination, alkylation, oxidation, and deamination. This repair mechanism involves the following sequence of events:

- Recognition of abnormal bases by specific **glycosylases** that cleave the altered DNA bases from the parent DNA molecule, leaving an empty sugar-phosphate site called an apurinic/apyrimidinic site (AP).
- Next, an **AP endonuclease** nicks the 5' end of the AP site before a deoxyribose phosphate **lyase** (or flap endonuclease) enzyme subsequently completes extraction of the remaining sugar-phosphate backbone.
- **DNA polymerase** then fills the gap with the correct nucleotide(s), and the final nick is sealed by a **ligase** enzyme.

Educational objective:

Base excision repair is used to correct single-base DNA defects induced spontaneously or by exogenous chemicals. In this process, glycosylases remove the defective base, and the corresponding empty sugar-phosphate site is cleaved and removed by the action of endonuclease and lyase. DNA polymerase then replaces the missing nucleotide, and ligase seals the final remaining nick.

References

- Overview of base excision repair biochemistry.

Genetics	Genetics (General Principles)	Dna structure & function
Subject	System	Topic

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A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most
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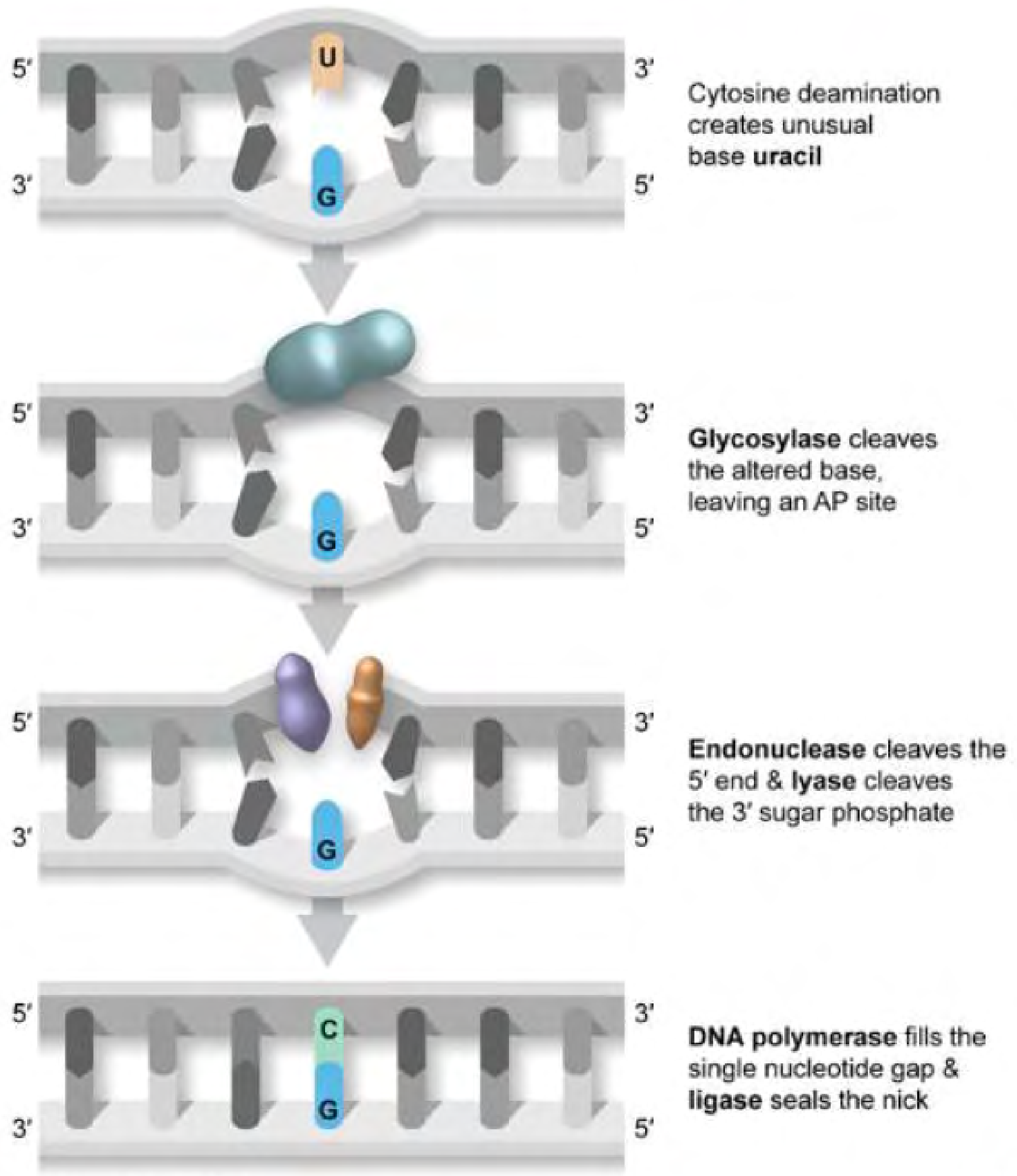
Base excision repair



Cytosine deamination creates unusual base **uracil**

Glycosylase cleaves the altered base, leaving an AP site

Endonuclease cleaves the 5′ end & **lyase** cleaves the 3′ sugar phosphate

DNA polymerase fills the single nucleotide gap & **ligase** seals the nick

AP = apurinic/apyrimidinic.

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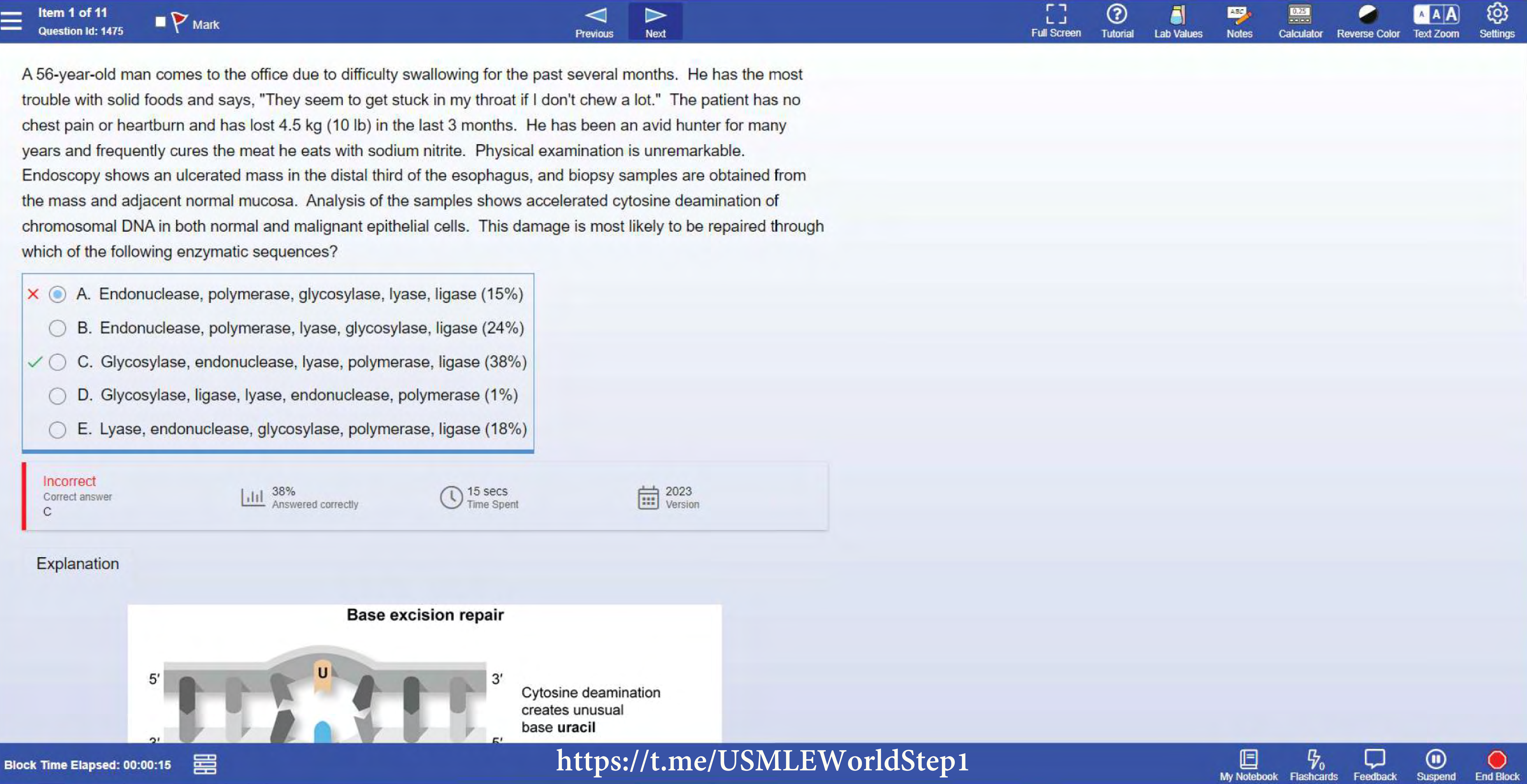
creates unusual
base **uracil**



Item 1 of 11
Question Id: 1475
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

- ✗ ● A. Endonuclease, polymerase, glycosylase, lyase, ligase (15%)
- ○ B. Endonuclease, polymerase, lyase, glycosylase, ligase (24%)
- ✓ ○ C. Glycosylase, endonuclease, lyase, polymerase, ligase (38%)
- ○ D. Glycosylase, ligase, lyase, endonuclease, polymerase (1%)
- ○ E. Lyase, endonuclease, glycosylase, polymerase, ligase (18%)

Incorrect
Correct answer
C

38%
Answered correctly

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2023
Version

Explanation

Base excision repair

Cytosine deamination creates unusual base **uracil**

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Flashcards
Feedback
Suspend
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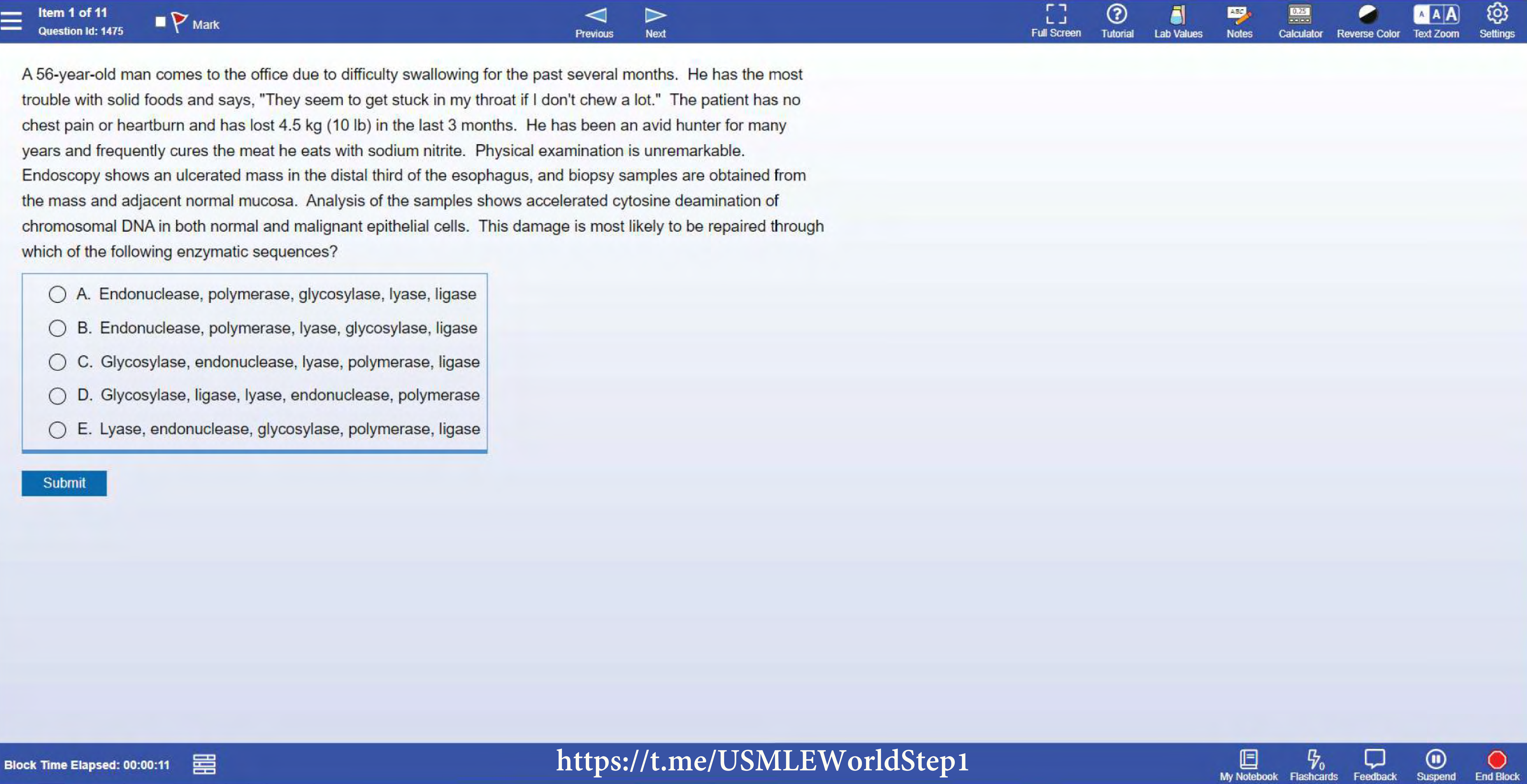
Item 1 of 11
Question Id: 1475
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ B. Endonuclease, polymerase, lyase, glycosylase, ligase
○ C. Glycosylase, endonuclease, lyase, polymerase, ligase
○ D. Glycosylase, ligase, lyase, endonuclease, polymerase
○ E. Lyase, endonuclease, glycosylase, polymerase, ligase

Submit
Block Time Elapsed: 00:00:11
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 40 of 40
Question Id: 1412
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

(Choice B) One or more complete codons (genetic triplet codes) are removed in an in-frame deletion, which does not affect the reading frame of subsequent codons. This patient's 28-base pair deletion is not divisible by 3, so it will result in a reading frame shift.

(Choices C and D) Missense and nonsense mutations are due to single base substitutions that result in the placement of an incorrect amino acid or introduction of a premature stop codon, respectively. These mutations occur in exons and affect protein translation. However, in this scenario, **gel electrophoresis** is being performed on **cDNA (not protein)** and the results indicate the **length of the mature RNA transcript**. Termination of RNA transcription occurs by specific sequences in the 3' untranslated region that cause RNA hairpin loop formation and/or recruitment of termination factors. As a result, point mutations in the exons of a gene (such as those responsible for causing nonsense mutations) are unlikely to affect total mRNA (cDNA) size.

(Choice E) Silent mutations can occur in both coding and noncoding regions, but they do not alter protein quantity or function and do not affect phenotype. This patient's mutation caused him to develop cystic fibrosis, so it is not a silent mutation.

(Choice F) Trinucleotide expansions increase the number of trinucleotide repeats in the coding region of a gene, often resulting in large proteins with abnormal function. This patient's abnormal *CFTR* gene is shorter (not longer) than the normal gene from his sibling, which indicates a deletion has occurred.

Educational objective:

Deletion or addition of a number of bases that is not divisible by 3 in the coding region of a gene will cause a frameshift mutation. Frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins.

References

- The CFTR frameshift mutation 3905insT and its effect at transcript and protein level.

Genetics	Genetics (General Principles)	Mutations
Subject	System	Topic

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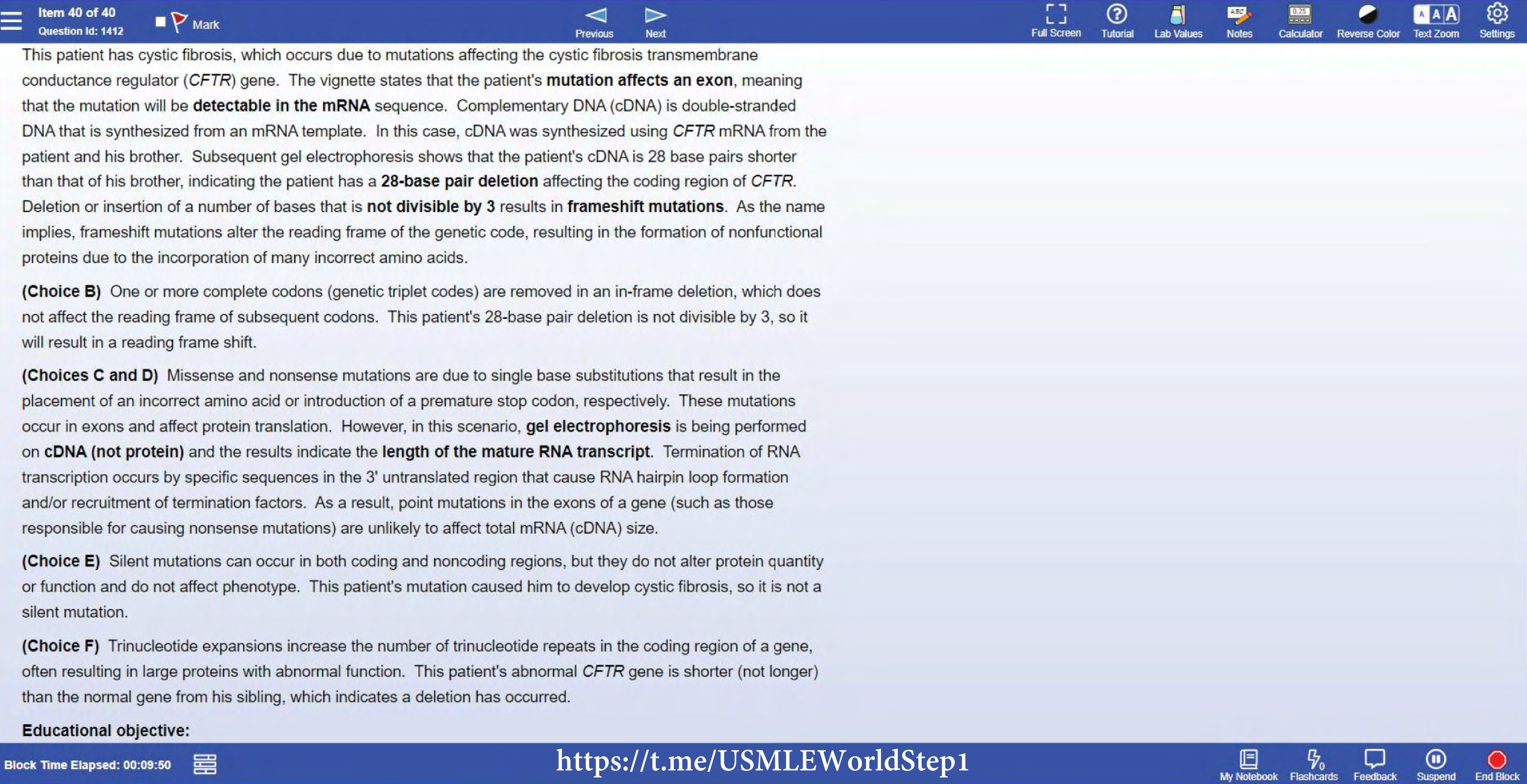

This patient has cystic fibrosis, which occurs due to mutations affecting the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The vignette states that the patient's **mutation affects an exon**, meaning that the mutation will be **detectable in the mRNA** sequence. Complementary DNA (cDNA) is double-stranded DNA that is synthesized from an mRNA template. In this case, cDNA was synthesized using *CFTR* mRNA from the patient and his brother. Subsequent gel electrophoresis shows that the patient's cDNA is 28 base pairs shorter than that of his brother, indicating the patient has a **28-base pair deletion** affecting the coding region of *CFTR*. Deletion or insertion of a number of bases that is **not divisible by 3** results in **frameshift mutations**. As the name implies, frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins due to the incorporation of many incorrect amino acids.

(Choice B) One or more complete codons (genetic triplet codes) are removed in an in-frame deletion, which does not affect the reading frame of subsequent codons. This patient's 28-base pair deletion is not divisible by 3, so it will result in a reading frame shift.

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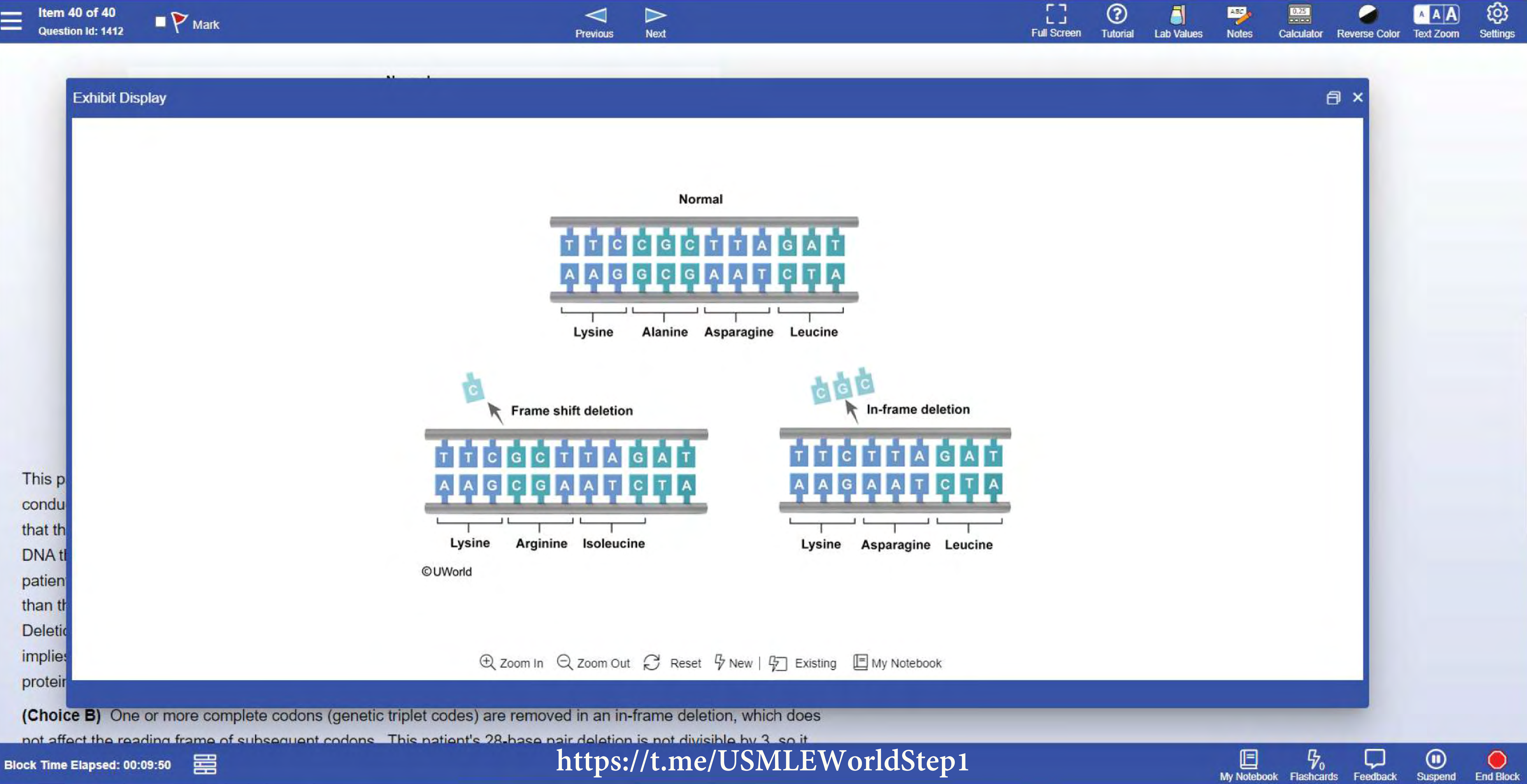
Educational objective:


Item 40 of 40
Question Id: 1412
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
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My Notebook
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Feedback
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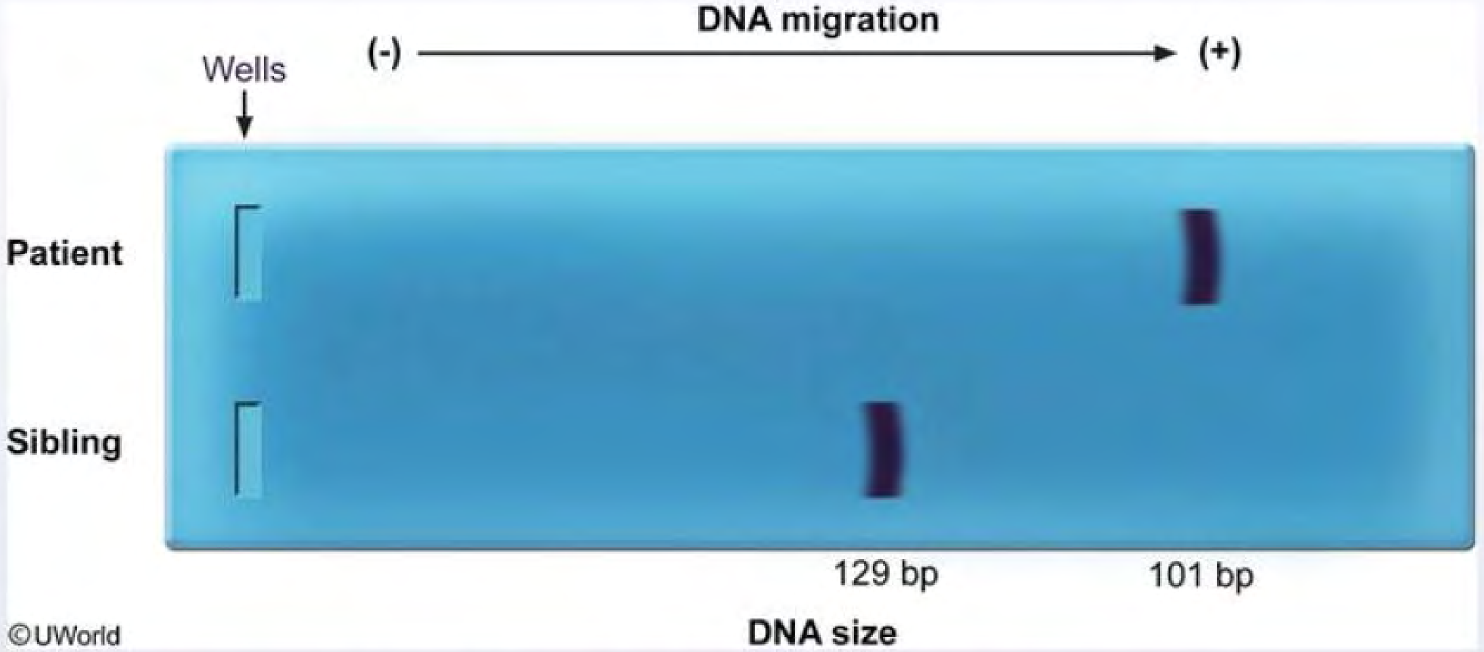
channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is synthesized. Amplified cDNA samples from both the patient and his healthy sibling are analyzed using gel electrophoresis and compared to DNA fragments of known size to determine base pair length. The results are shown below.



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Which of the following is most likely responsible for this patient's condition?

✓ ● A. Frameshift mutation (24%)
○ B. In-frame deletion (15%)
○ C. Missense mutation (10%)
○ D. Nonsense mutation (47%)
○ E. Silent mutation (0%)
○ F. Trinucleotide expansion (1%)

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24% Answered correctly
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channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is

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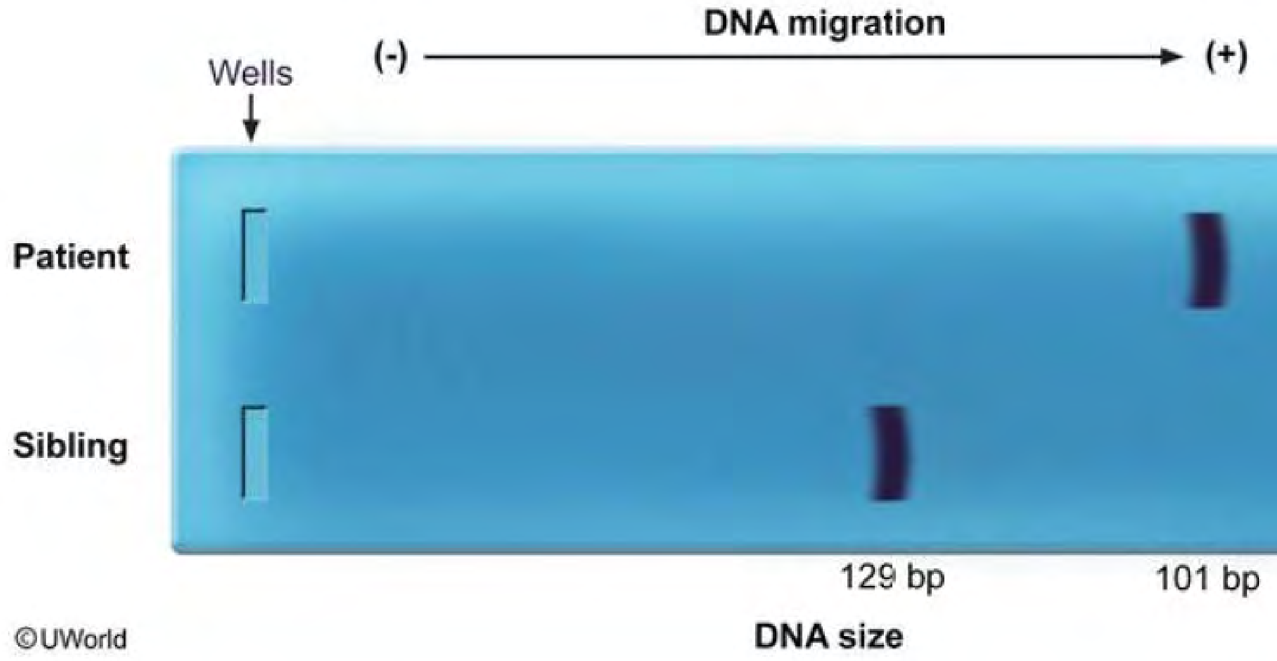
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DNA size
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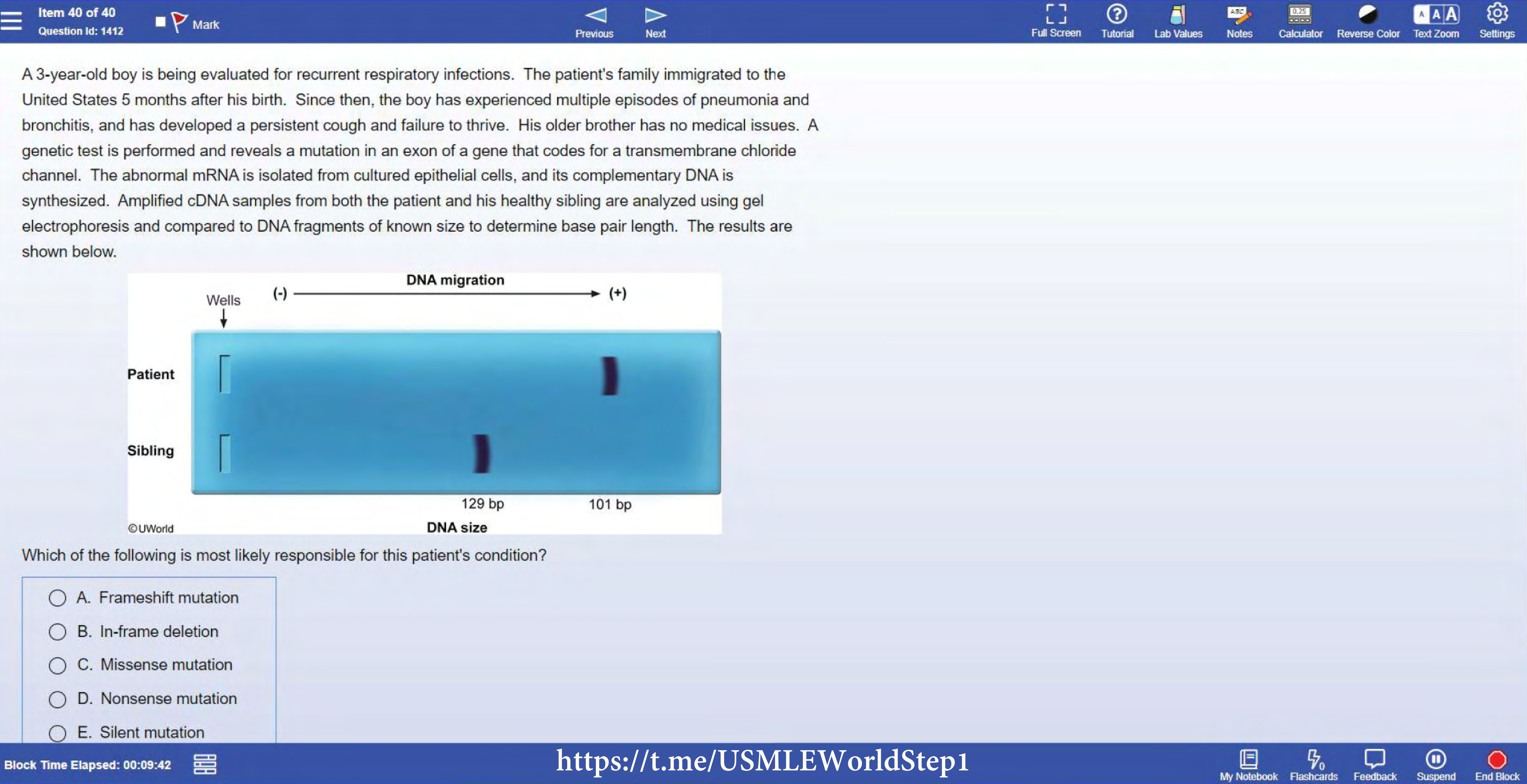
Item 40 of 40
Question Id: 1412
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 3-year-old boy is being evaluated for recurrent respiratory infections. The patient's family immigrated to the United States 5 months after his birth. Since then, the boy has experienced multiple episodes of pneumonia and bronchitis, and has developed a persistent cough and failure to thrive. His older brother has no medical issues. A genetic test is performed and reveals a mutation in an exon of a gene that codes for a transmembrane chloride channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is synthesized. Amplified cDNA samples from both the patient and his healthy sibling are analyzed using gel electrophoresis and compared to DNA fragments of known size to determine base pair length. The results are shown below.

DNA migration
Wells
(-)
(+)
Patient
Sibling
129 bp
101 bp
DNA size
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Which of the following is most likely responsible for this patient's condition?

○ A. Frameshift mutation
○ B. In-frame deletion
○ C. Missense mutation
○ D. Nonsense mutation
○ E. Silent mutation

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My Notebook
Flashcards
Feedback
Suspend
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DNA replication normally occurs during the S (synthesis) phase of the cell cycle and is initiated as follows:

- First, the origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA).
- Helicase subsequently binds to ssDNA at the origin of replication and moves into the replication fork, where it facilitates separation and unwinding of dsDNA.
- Then ssDNA binding proteins bind to and stabilize the unwound strands as they move away from the replication fork, preventing them from reannealing **(Choice C)**.
- DNA unwinding induces strain on the DNA segment upstream of the helicases (positive supercoiling), and topoisomerase (DNA gyrase) relieves this tension by introducing transient single- or double-stranded nicks in the DNA **(Choice A)**.

(Choice D) Before DNA polymerase can begin synthesizing DNA, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase).

(Choice E) DNA polymerase synthesizes new daughter DNA strands in the 5′ to 3′ direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously (ie, multiple short DNA fragments called Okazaki fragments).

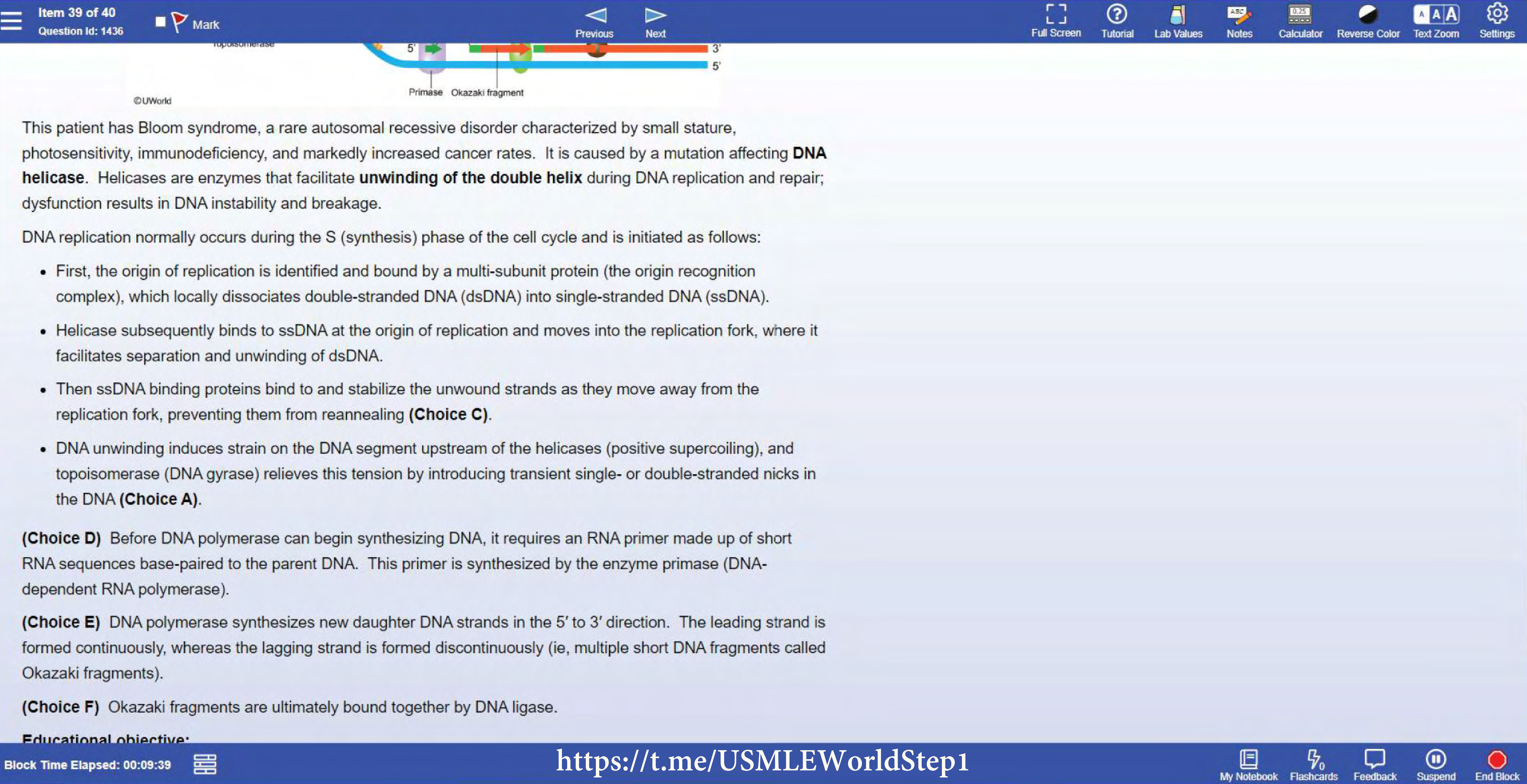
(Choice F) Okazaki fragments are ultimately bound together by DNA ligase.

Educational objective:

During DNA replication and repair, helicase mediates the continuous unwinding of double-stranded DNA at the replication fork.

References

- The replication fork: understanding the eukaryotic replication machinery and the challenges to genome duplication.


Item 39 of 40
Question Id: 1436
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Topoisomerase
5'
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Primase
Okazaki fragment
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My Notebook
Flashcards
Feedback
Suspend
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This patient has Bloom syndrome, a rare autosomal recessive disorder characterized by small stature, photosensitivity, immunodeficiency, and markedly increased cancer rates. It is caused by a mutation affecting **DNA helicase**. Helicases are enzymes that facilitate **unwinding of the double helix** during DNA replication and repair; dysfunction results in DNA instability and breakage.

DNA replication normally occurs during the S (synthesis) phase of the cell cycle and is initiated as follows:

- First, the origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA).
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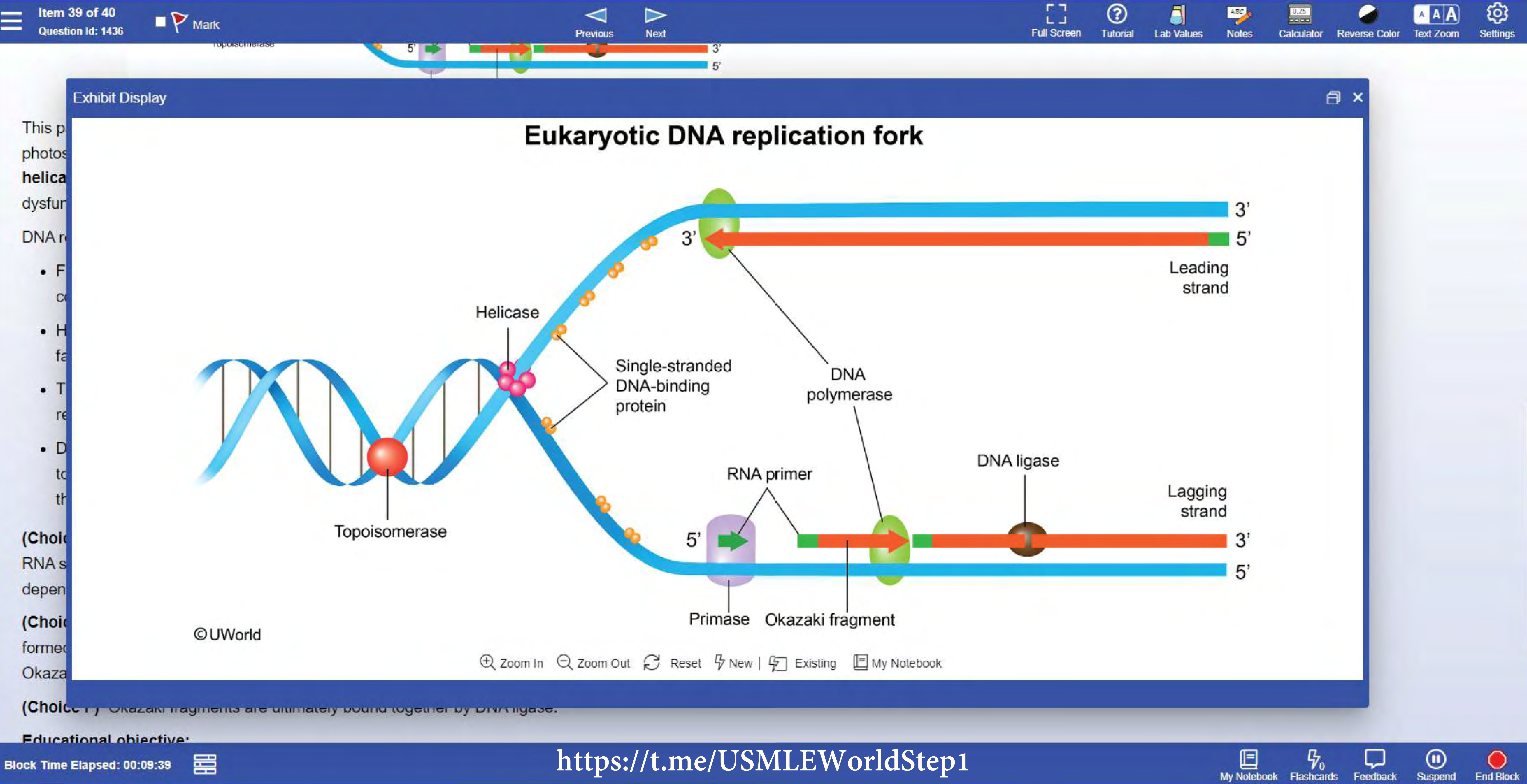
(Choice F) Okazaki fragments are ultimately bound together by DNA ligase.

Educational objective:


Item 39 of 40
Question Id: 1436
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Eukaryotic DNA replication fork
3'
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3'
Leading strand
Helicase
Single-stranded DNA-binding protein
DNA polymerase
Topoisomerase
RNA primer
DNA ligase
Lagging strand
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Primase
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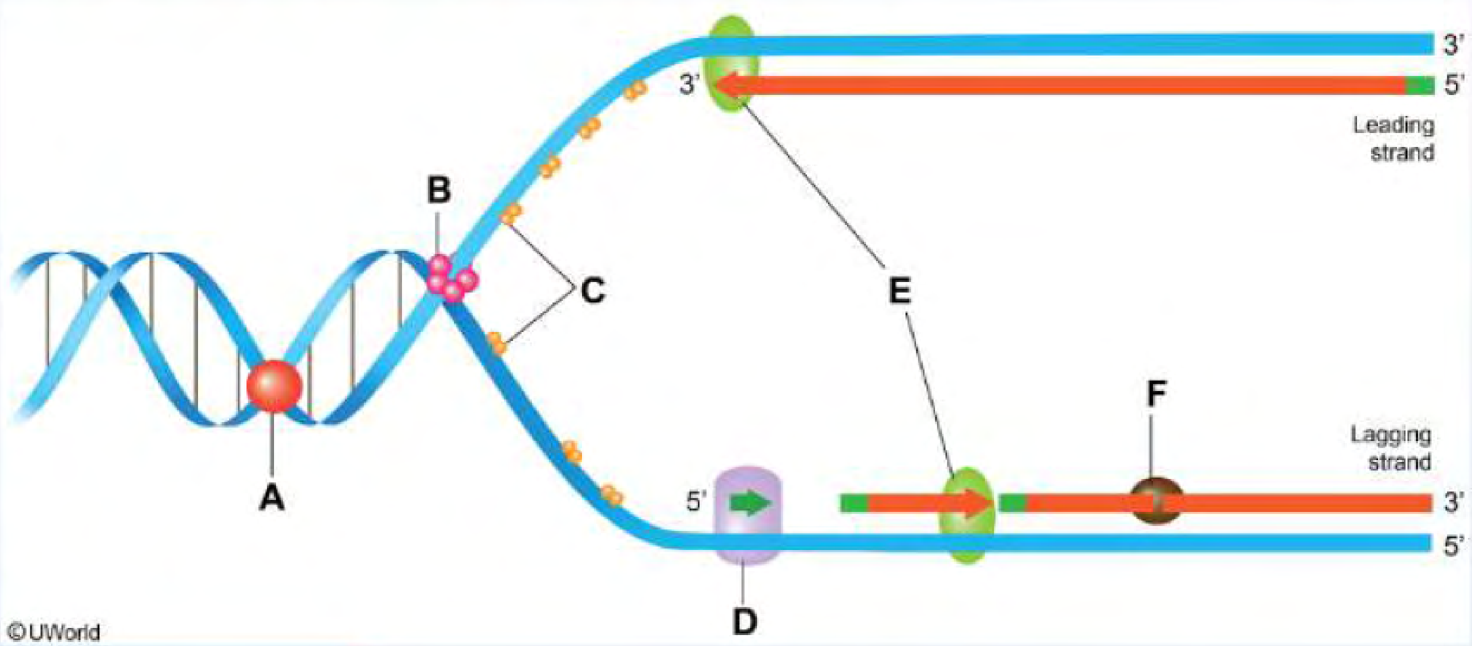
(Choice F) Okazaki fragments are ultimately bound together by DNA ligase.

Educational objective:

A 13-year-old boy is evaluated for a possible inherited genetic defect. He has growth retardation, microcephaly, sun-sensitive skin, and recurrent infections. The patient is the second-born child of 2 first cousins. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene, which codes for a DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork diagram shown below?



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- ○ A. A
- ✓ ○ B. B
- ✗ ● C. C
- ○ D. D
- ○ E. E
- ○ F. F

Incorrect
Correct answer
B

Collecting Statistics

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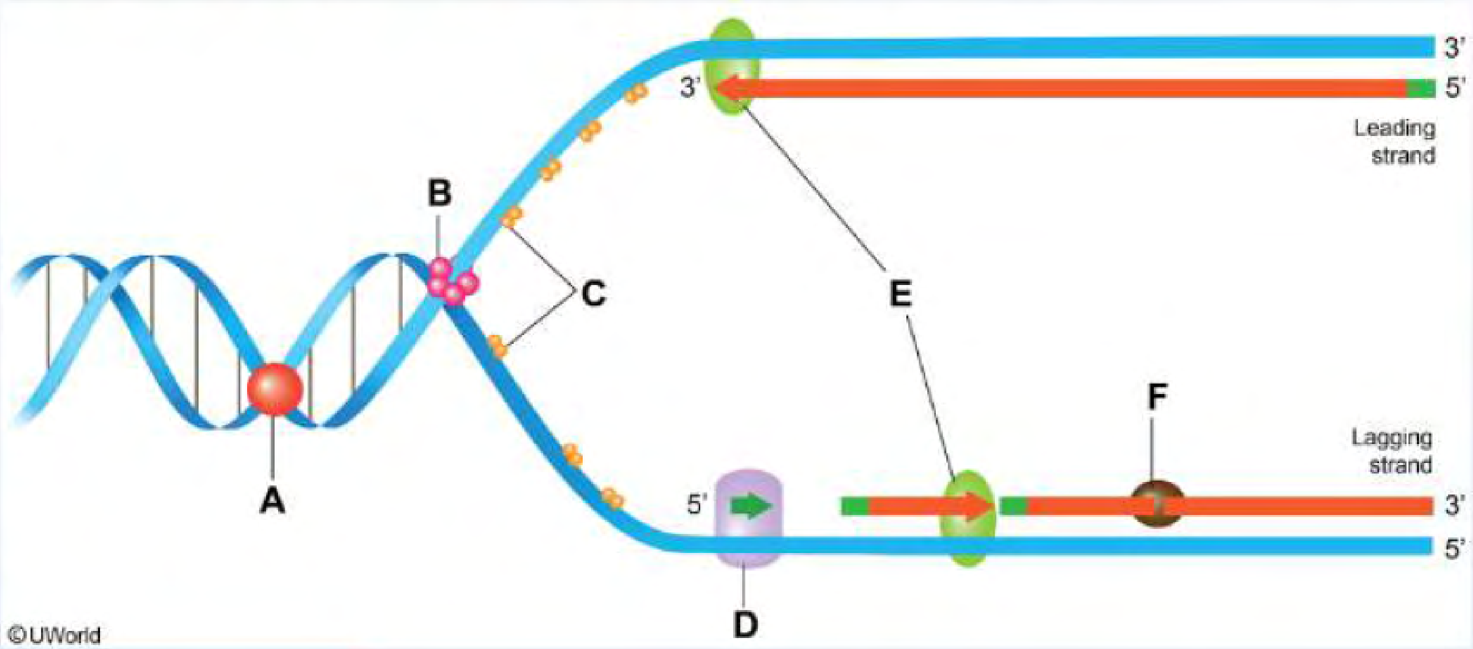
A 13-year-old boy is evaluated for a possible inherited genetic defect. He has growth retardation, microcephaly, sun-sensitive skin, and recurrent infections. The patient is the second-born child of 2 first cousins. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene, which codes for a DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork diagram shown below?



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○ A. A
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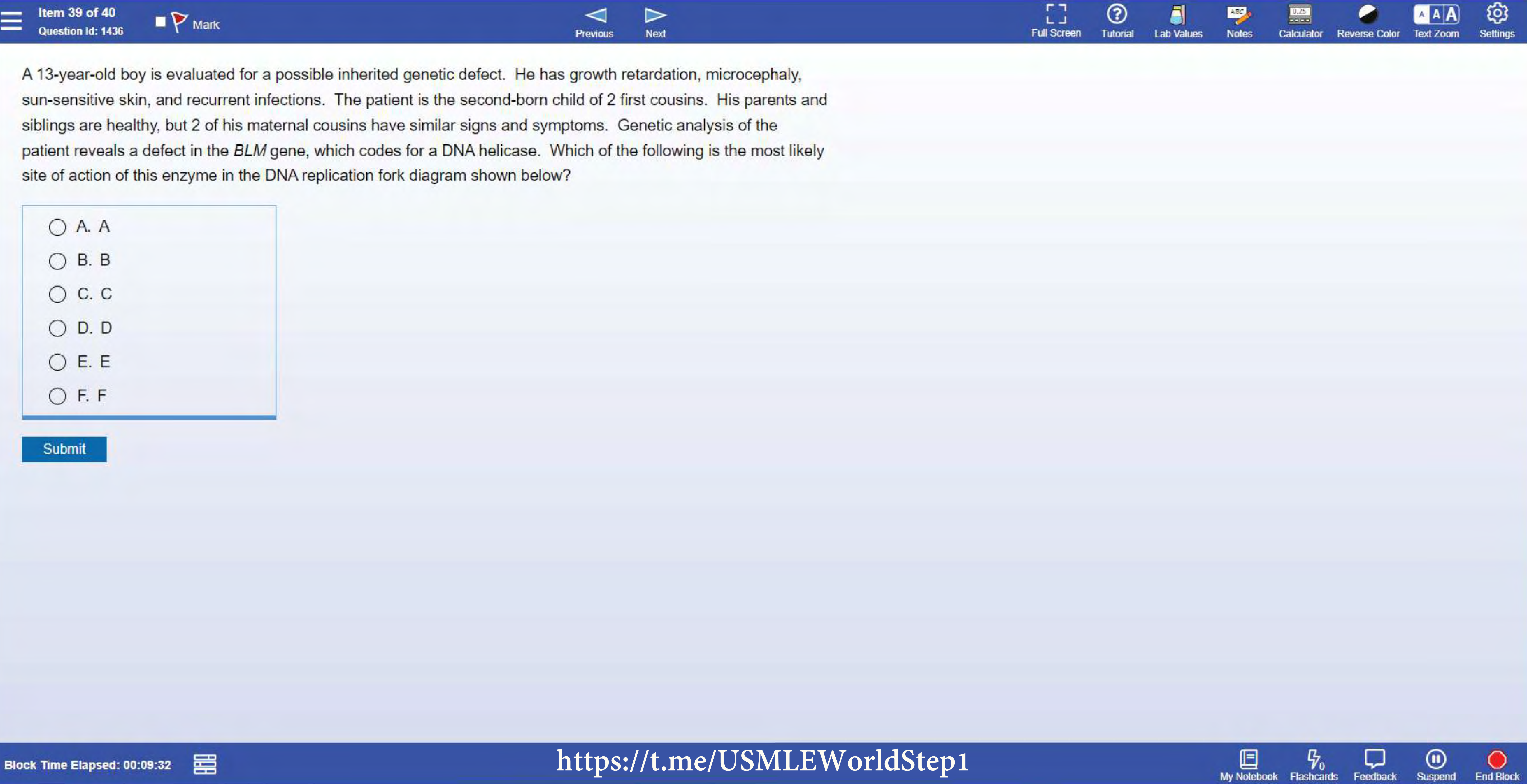
Item 39 of 40
Question Id: 1436
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 13-year-old boy is evaluated for a possible inherited genetic defect. He has growth retardation, microcephaly, sun-sensitive skin, and recurrent infections. The patient is the second-born child of 2 first cousins. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene, which codes for a DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork diagram shown below?

○ A. A

○ B. B

○ C. C

○ D. D

○ E. E

○ F. F

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Block Time Elapsed: 00:09:32
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 38 of 40
Question Id: 1480
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:09:32
My Notebook
Flashcards
Feedback
Suspend
End Block

(Choice A) The amino acid derivative γ-aminobutyrate (GABA) is a well-known inhibitor of presynaptic transmission in the retina and central nervous system. GABA is formed from glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase.

(Choice B) Glutamine is the major amino acid in the blood because it transports excess ammonia from peripheral tissues to the kidney. In the nephron, the amide nitrogen is hydrolyzed by glutaminase to regenerate glutamate and a free ammonium ion, which can then be excreted in the urine.

(Choice C) Deficiencies of vitamins B$_6$, B$_{12}$, and folate (B$_9$) are associated with hyperhomocysteinemia, which in turn is associated with atherosclerosis and thrombotic events.

(Choice D) Orotic acid is overproduced when a block in the urea cycle leads to excess carbamoyl phosphate, which is metabolized by dihydroorotate dehydrogenase to orotic acid. Excessive amounts of orotic acid are usually found in citrullinemia and ornithine transcarbamylase deficiency. These urea cycle disorders are also accompanied by hyperammonemia.

(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also undergoes neuronal reuptake.

Educational objective:

Arginase is a urea cycle enzyme that produces urea and ornithine from arginine. Arginase deficiency results in progressive spastic diplegia, growth delay, and abnormal movements. Treatment includes an arginine-free, low-protein diet.

References

- Arginase-1 deficiency.
- Arginase Deficiency.

Biochemistry	Biochemistry (General Principles)	Urea cycle
Subject	System	Topic

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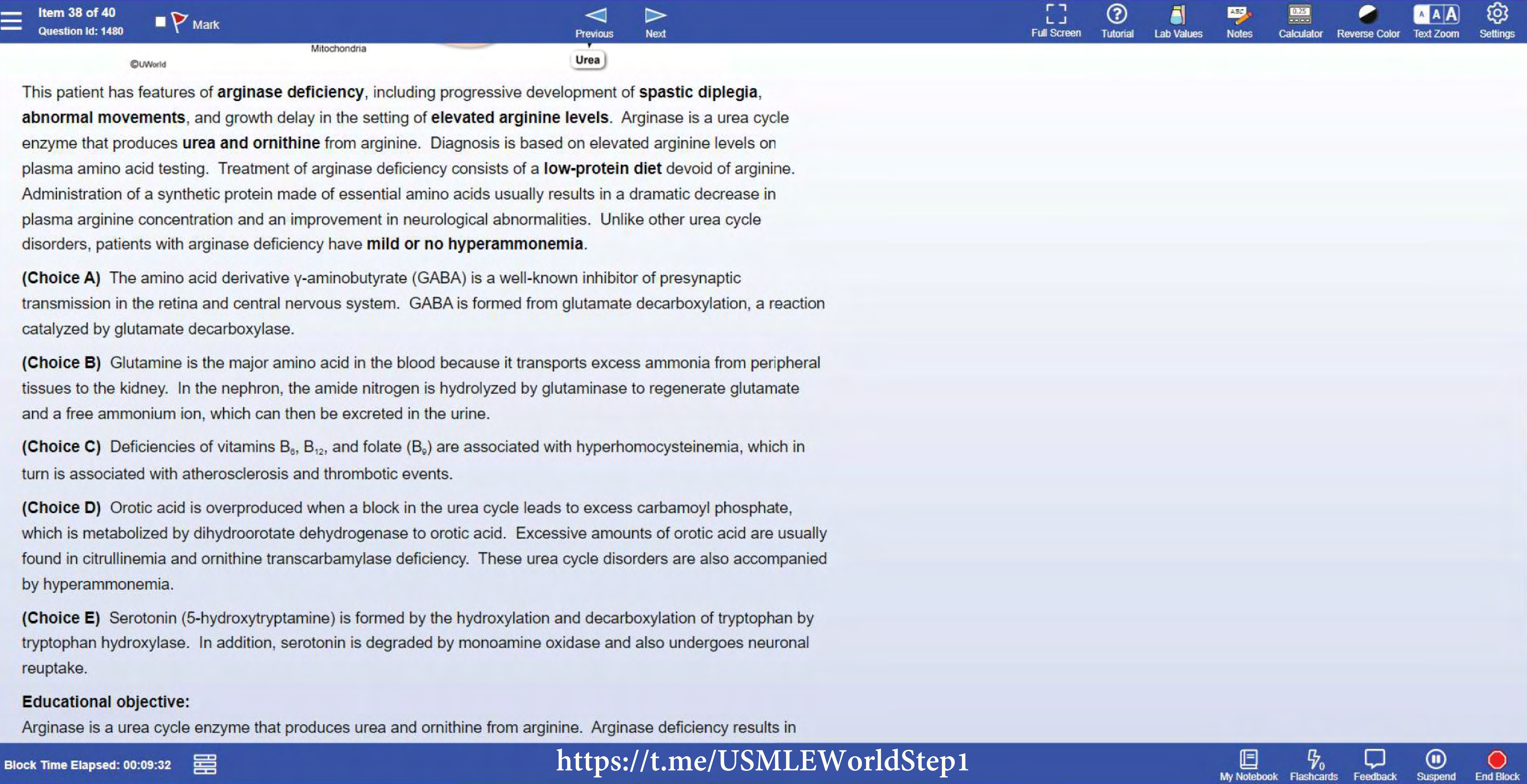

This patient has features of **arginase deficiency**, including progressive development of **spastic diplegia**, **abnormal movements**, and growth delay in the setting of **elevated arginine levels**. Arginase is a urea cycle enzyme that produces **urea and ornithine** from arginine. Diagnosis is based on elevated arginine levels on plasma amino acid testing. Treatment of arginase deficiency consists of a **low-protein diet** devoid of arginine. Administration of a synthetic protein made of essential amino acids usually results in a dramatic decrease in plasma arginine concentration and an improvement in neurological abnormalities. Unlike other urea cycle disorders, patients with arginase deficiency have **mild or no hyperammonemia**.

(Choice A) The amino acid derivative γ-aminobutyrate (GABA) is a well-known inhibitor of presynaptic transmission in the retina and central nervous system. GABA is formed from glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase.

(Choice B) Glutamine is the major amino acid in the blood because it transports excess ammonia from peripheral tissues to the kidney. In the nephron, the amide nitrogen is hydrolyzed by glutaminase to regenerate glutamate and a free ammonium ion, which can then be excreted in the urine.

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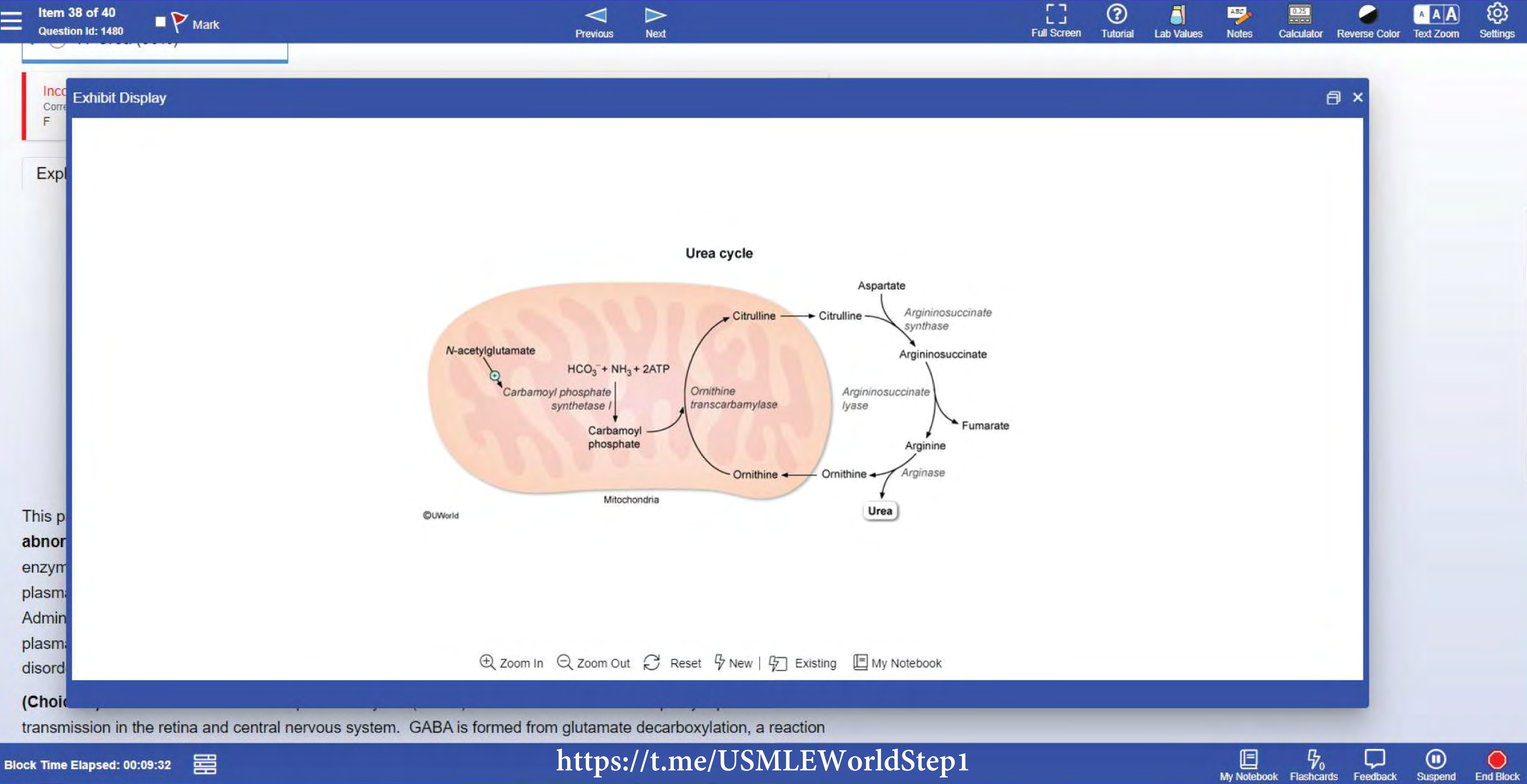
(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also undergoes neuronal reuptake.

Educational objective:

Arginase is a urea cycle enzyme that produces urea and ornithine from arginine. Arginase deficiency results in


Item 38 of 40
Question Id: 1480
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Urea cycle
Aspartate
Citrulline
Citrulline
Argininosuccinate synthase
Argininosuccinate
N-acetylglutamate
HCO3− + NH3 + 2ATP
Carbamoyl phosphate synthetase I
Carbamoyl phosphate
Ornithine transcarbamylase
Argininosuccinate lyase
Fumarate
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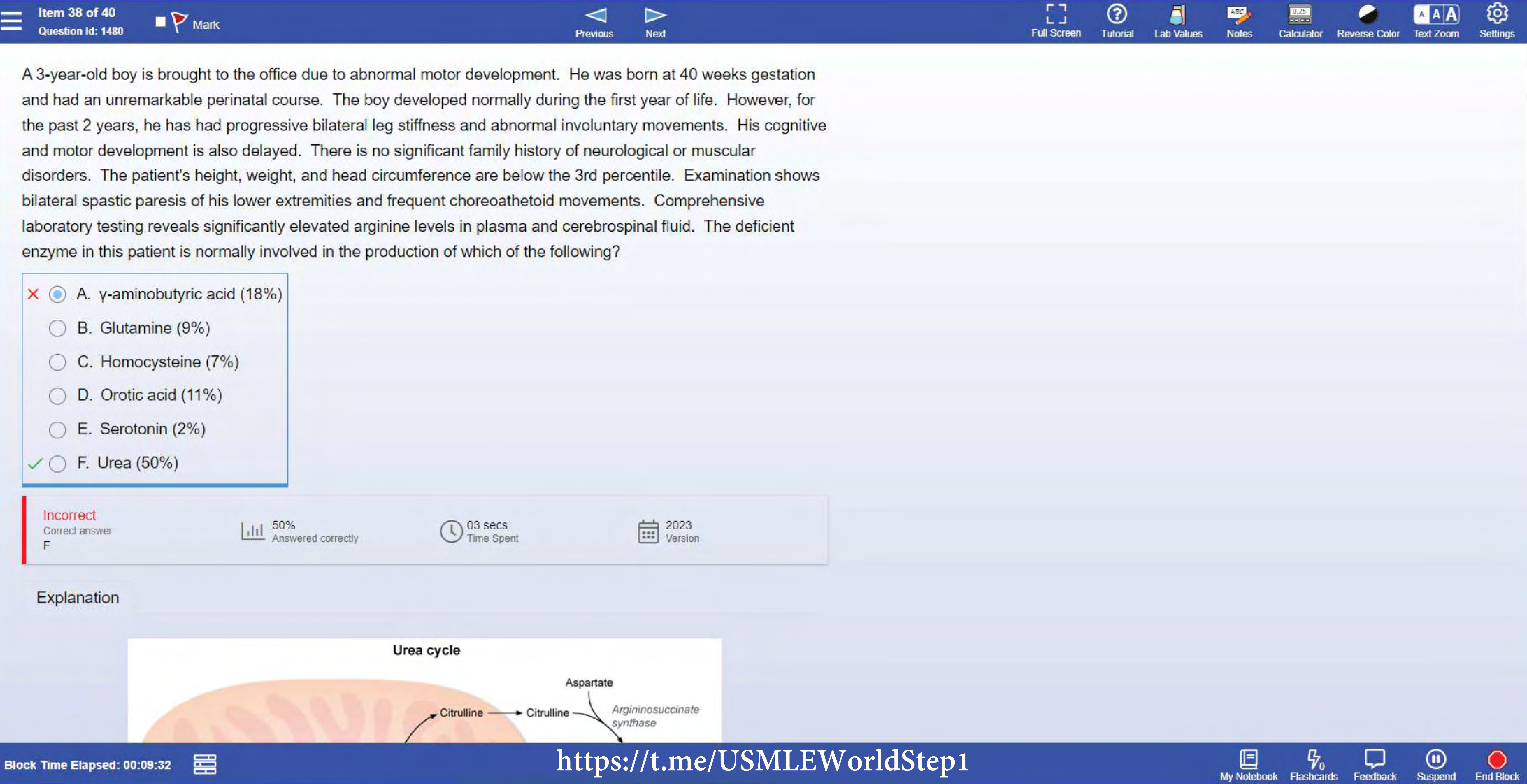
Item 38 of 40
Question Id: 1480
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 3-year-old boy is brought to the office due to abnormal motor development. He was born at 40 weeks gestation and had an unremarkable perinatal course. The boy developed normally during the first year of life. However, for the past 2 years, he has had progressive bilateral leg stiffness and abnormal involuntary movements. His cognitive and motor development is also delayed. There is no significant family history of neurological or muscular disorders. The patient's height, weight, and head circumference are below the 3rd percentile. Examination shows bilateral spastic paresis of his lower extremities and frequent choreoathetoid movements. Comprehensive laboratory testing reveals significantly elevated arginine levels in plasma and cerebrospinal fluid. The deficient enzyme in this patient is normally involved in the production of which of the following?

- ✗ ● A. γ-aminobutyric acid (18%)
- ○ B. Glutamine (9%)
- ○ C. Homocysteine (7%)
- ○ D. Orotic acid (11%)
- ○ E. Serotonin (2%)
- ✓ ○ F. Urea (50%)

Incorrect
Correct answer
F

50%
Answered correctly

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Version

Explanation

Urea cycle

Aspartate
Citrulline
Citrulline
Argininosuccinate synthase

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My Notebook
Flashcards
Feedback
Suspend
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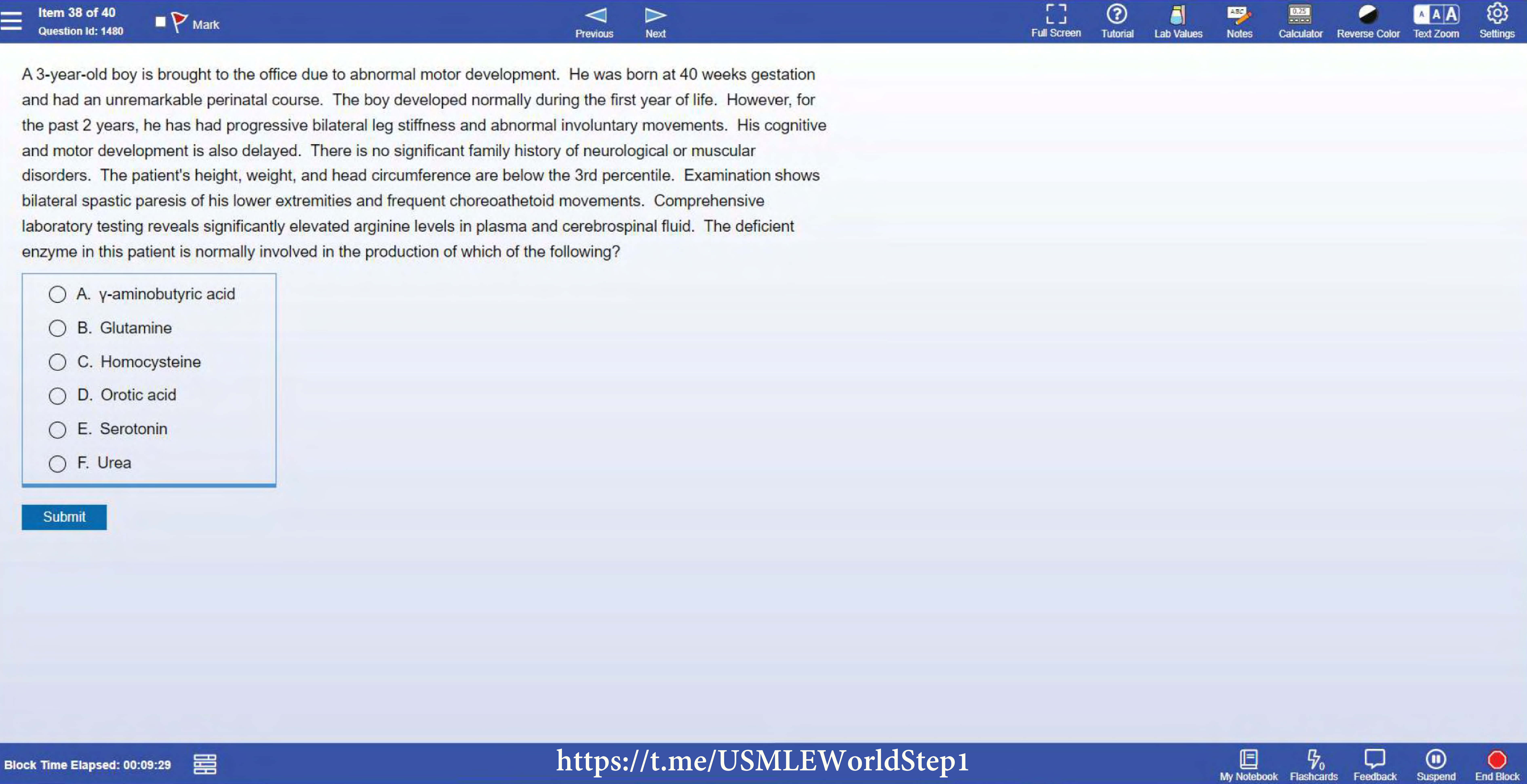
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Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 38 of 40
Question Id: 1480

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○ B. Glutamine
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○ D. Orotic acid
○ E. Serotonin
○ F. Urea

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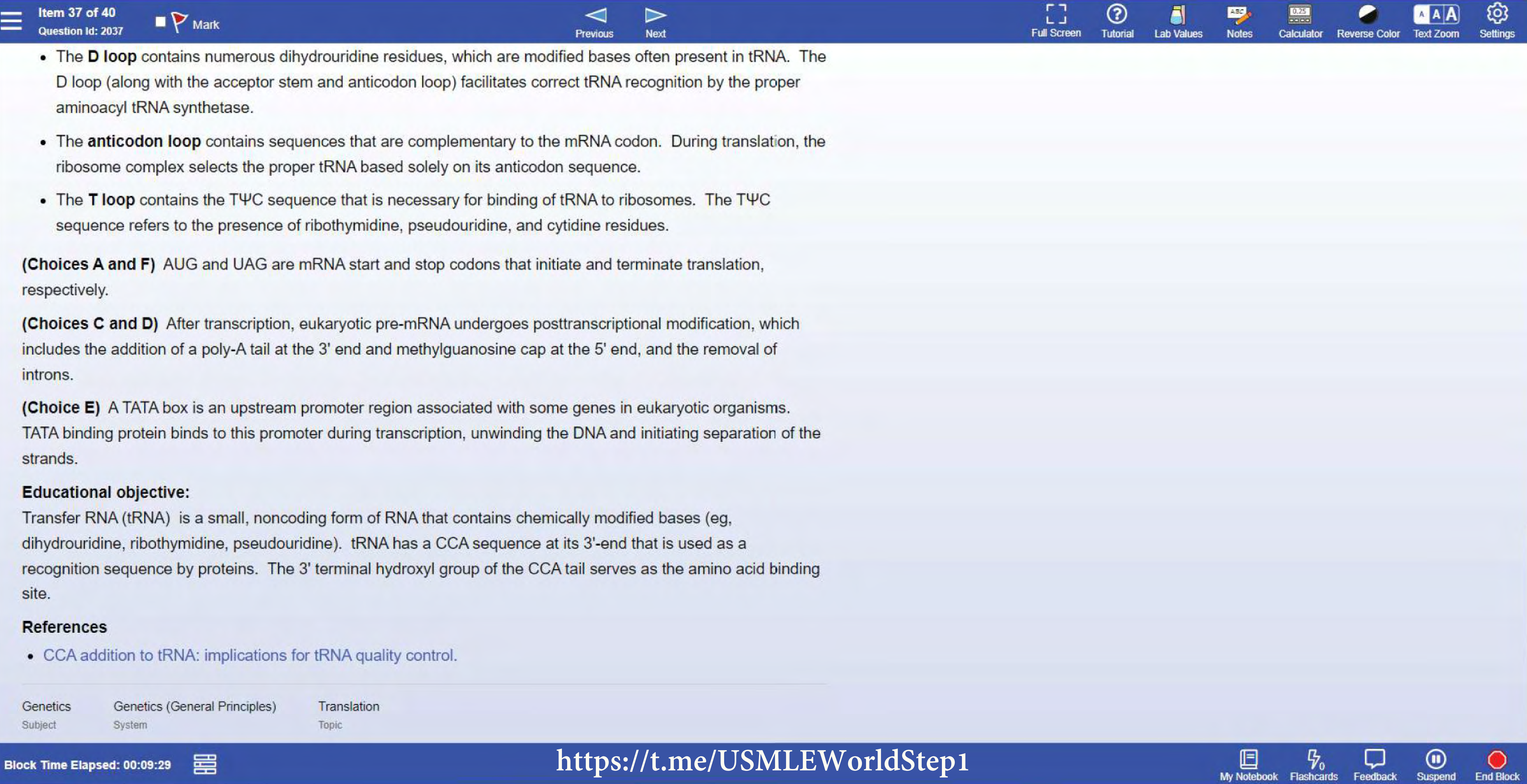

- The **D loop** contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- The **anticodon loop** contains sequences that are complementary to the mRNA codon. During translation, the ribosome complex selects the proper tRNA based solely on its anticodon sequence.
- The **T loop** contains the TΨC sequence that is necessary for binding of tRNA to ribosomes. The TΨC sequence refers to the presence of ribothymidine, pseudouridine, and cytidine residues.

(Choices A and F) AUG and UAG are mRNA start and stop codons that initiate and terminate translation, respectively.

(Choices C and D) After transcription, eukaryotic pre-mRNA undergoes posttranscriptional modification, which includes the addition of a poly-A tail at the 3' end and methylguanosine cap at the 5' end, and the removal of introns.

(Choice E) A TATA box is an upstream promoter region associated with some genes in eukaryotic organisms. TATA binding protein binds to this promoter during transcription, unwinding the DNA and initiating separation of the strands.

Educational objective:

Transfer RNA (tRNA) is a small, noncoding form of RNA that contains chemically modified bases (eg, dihydrouridine, ribothymidine, pseudouridine). tRNA has a CCA sequence at its 3'-end that is used as a recognition sequence by proteins. The 3' terminal hydroxyl group of the CCA tail serves as the amino acid binding site.

References

- CCA addition to tRNA: implications for tRNA quality control.

Genetics	Genetics (General Principles)	Translation
Subject	System	Topic

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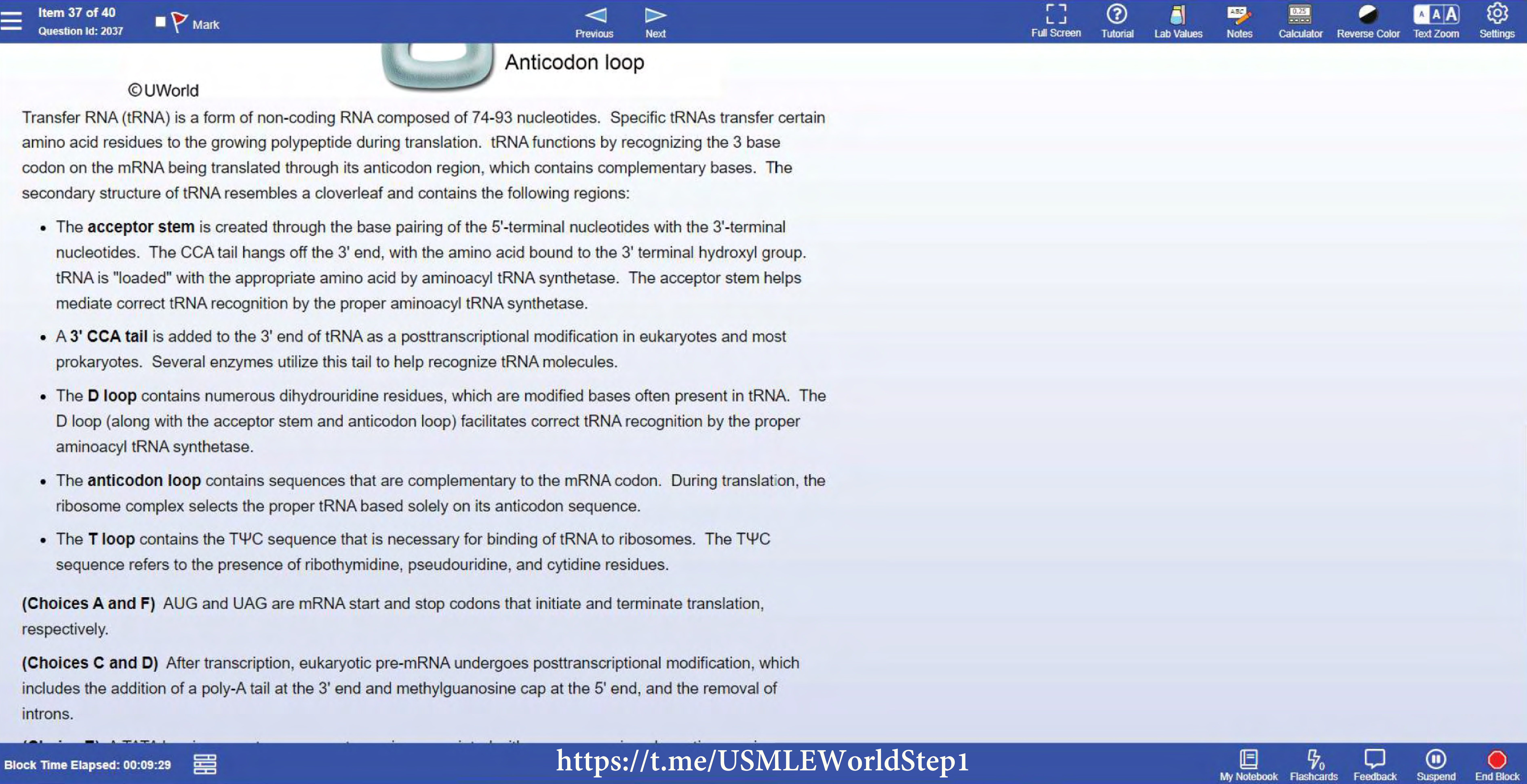
Item 37 of 40
Question Id: 2037
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Anticodon loop
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Block Time Elapsed: 00:09:29
My Notebook
Flashcards
Feedback
Suspend
End Block

Transfer RNA (tRNA) is a form of non-coding RNA composed of 74-93 nucleotides. Specific tRNAs transfer certain amino acid residues to the growing polypeptide during translation. tRNA functions by recognizing the 3 base codon on the mRNA being translated through its anticodon region, which contains complementary bases. The secondary structure of tRNA resembles a cloverleaf and contains the following regions:

- The **acceptor stem** is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. The CCA tail hangs off the 3' end, with the amino acid bound to the 3' terminal hydroxyl group. tRNA is "loaded" with the appropriate amino acid by aminoacyl tRNA synthetase. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- A **3' CCA tail** is added to the 3' end of tRNA as a posttranscriptional modification in eukaryotes and most prokaryotes. Several enzymes utilize this tail to help recognize tRNA molecules.
- The **D loop** contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- The **anticodon loop** contains sequences that are complementary to the mRNA codon. During translation, the ribosome complex selects the proper tRNA based solely on its anticodon sequence.
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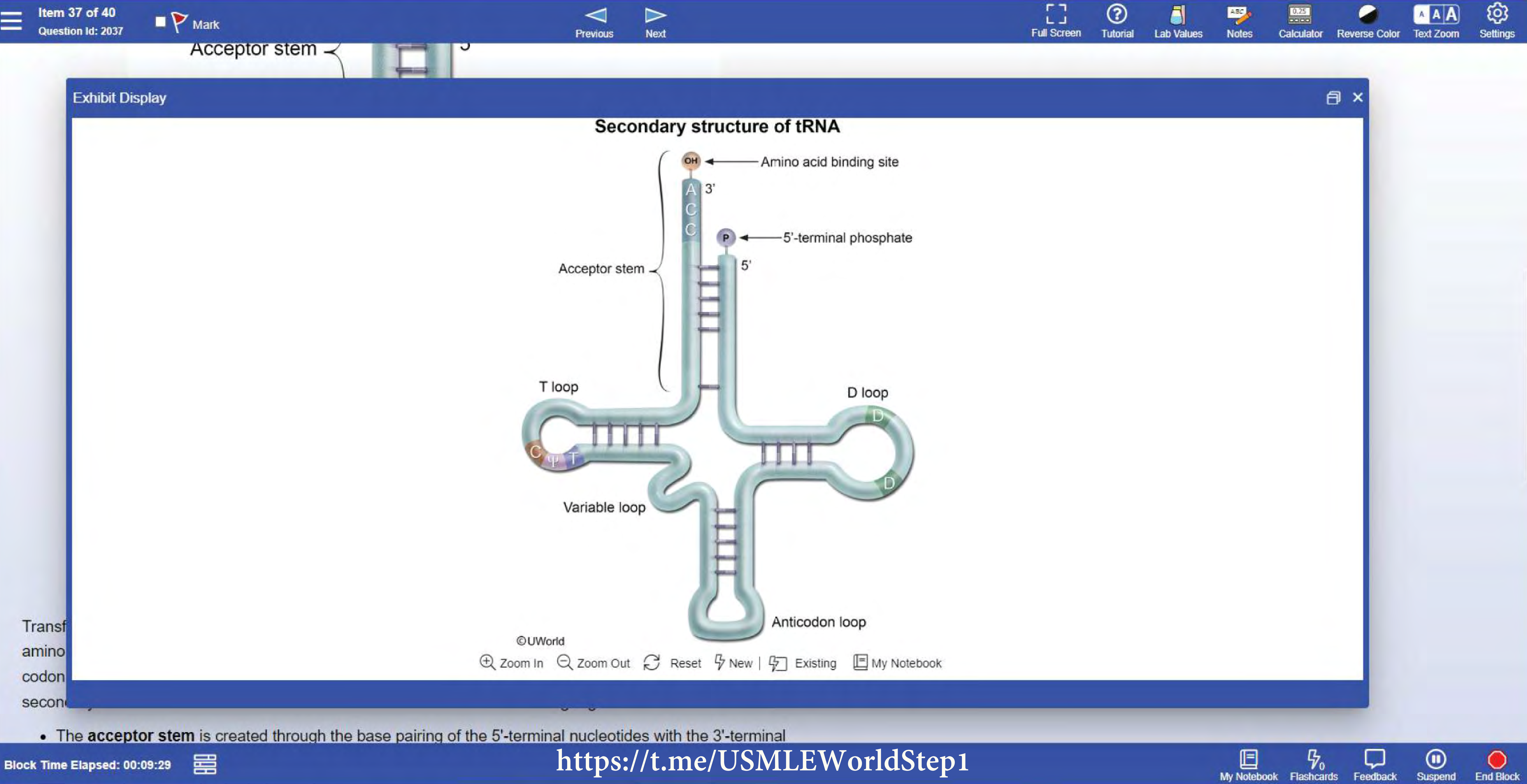
Item 37 of 40
Question Id: 2037
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Zoom In
Zoom Out
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My Notebook
Flashcards
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Suspend
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Secondary structure of tRNA

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- The **acceptor stem** is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal

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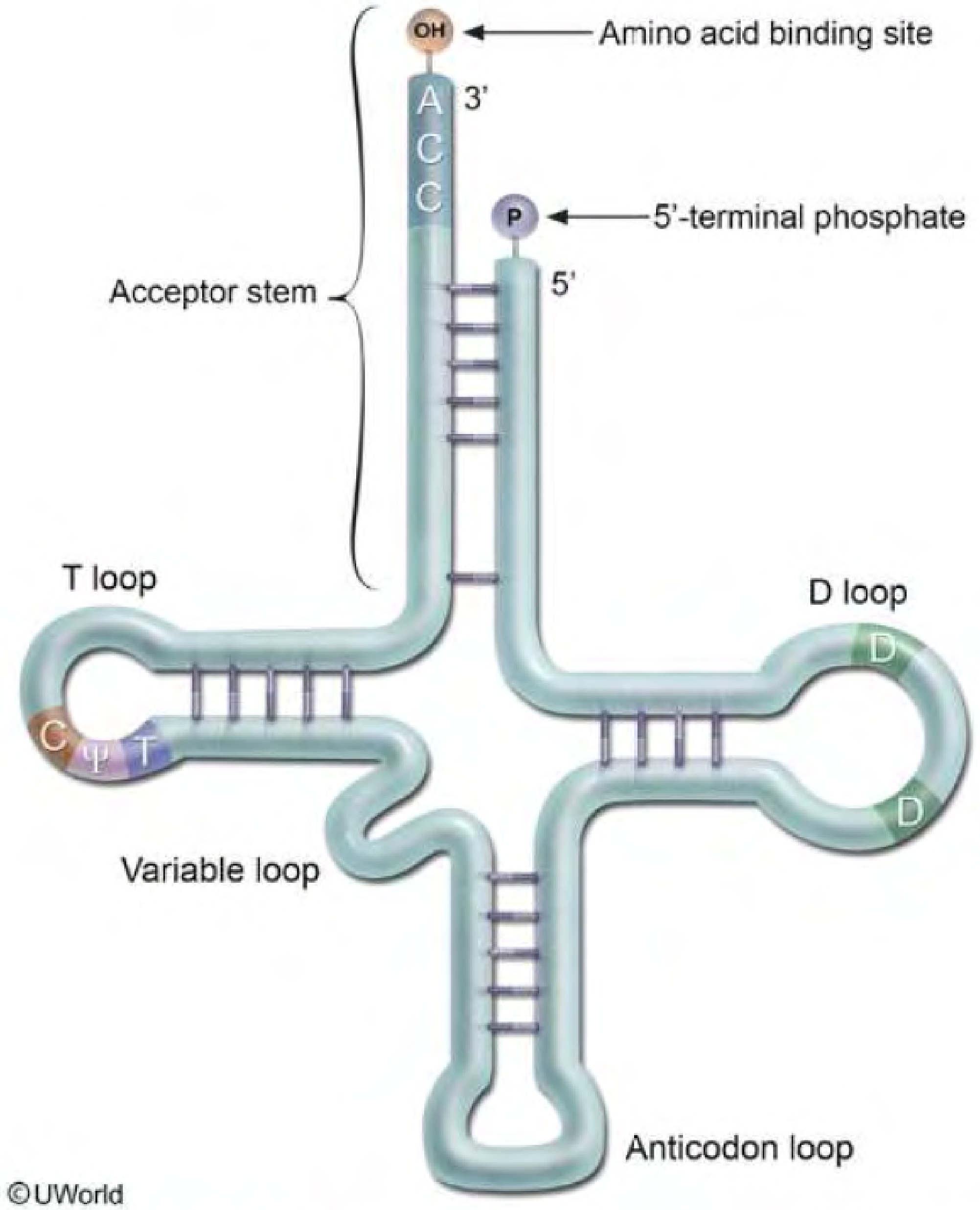
Secondary structure of tRNA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P
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Acceptor stem
T loop
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Anticodon loop

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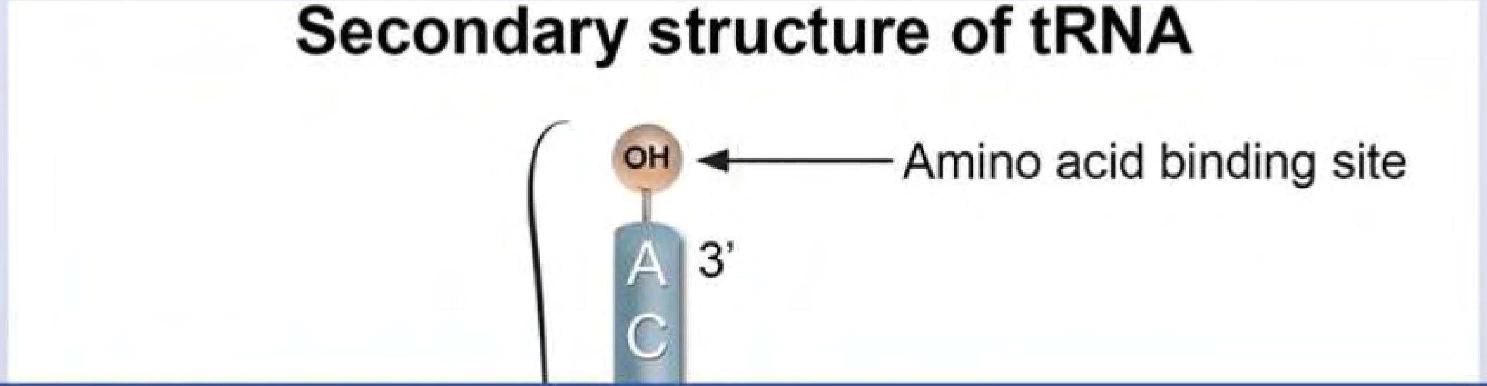
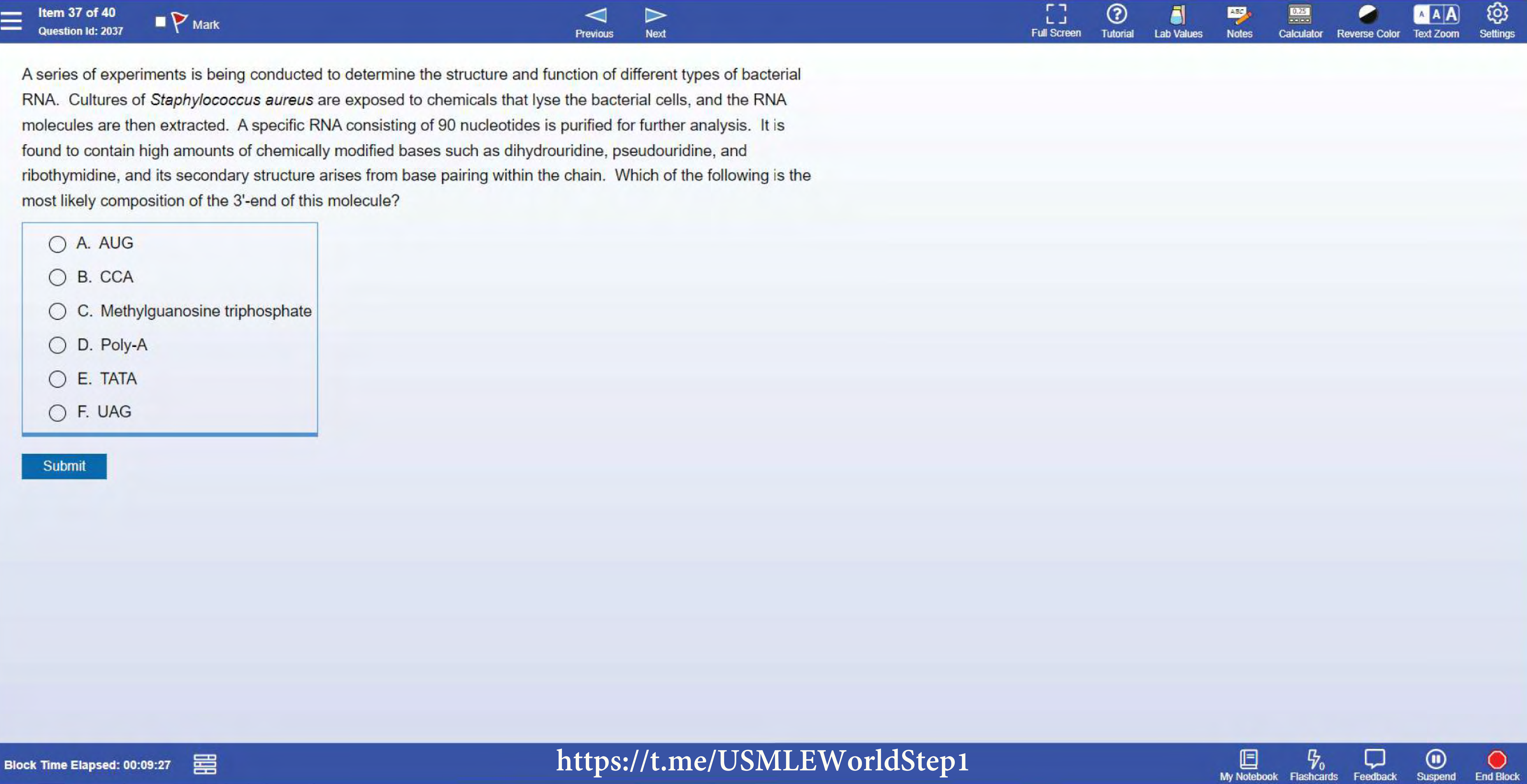
A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

- ○ A. AUG (5%)
- ✓ ● B. CCA (41%)
- ○ C. Methylguanosine triphosphate (5%)
- ○ D. Poly-A (30%)
- ○ E. TATA (3%)
- ○ F. UAG (12%)

Correct | 41% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation


Secondary structure of tRNA


Item 37 of 40
Question Id: 2037
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:09:27
My Notebook
Flashcards
Feedback
Suspend
End Block

A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

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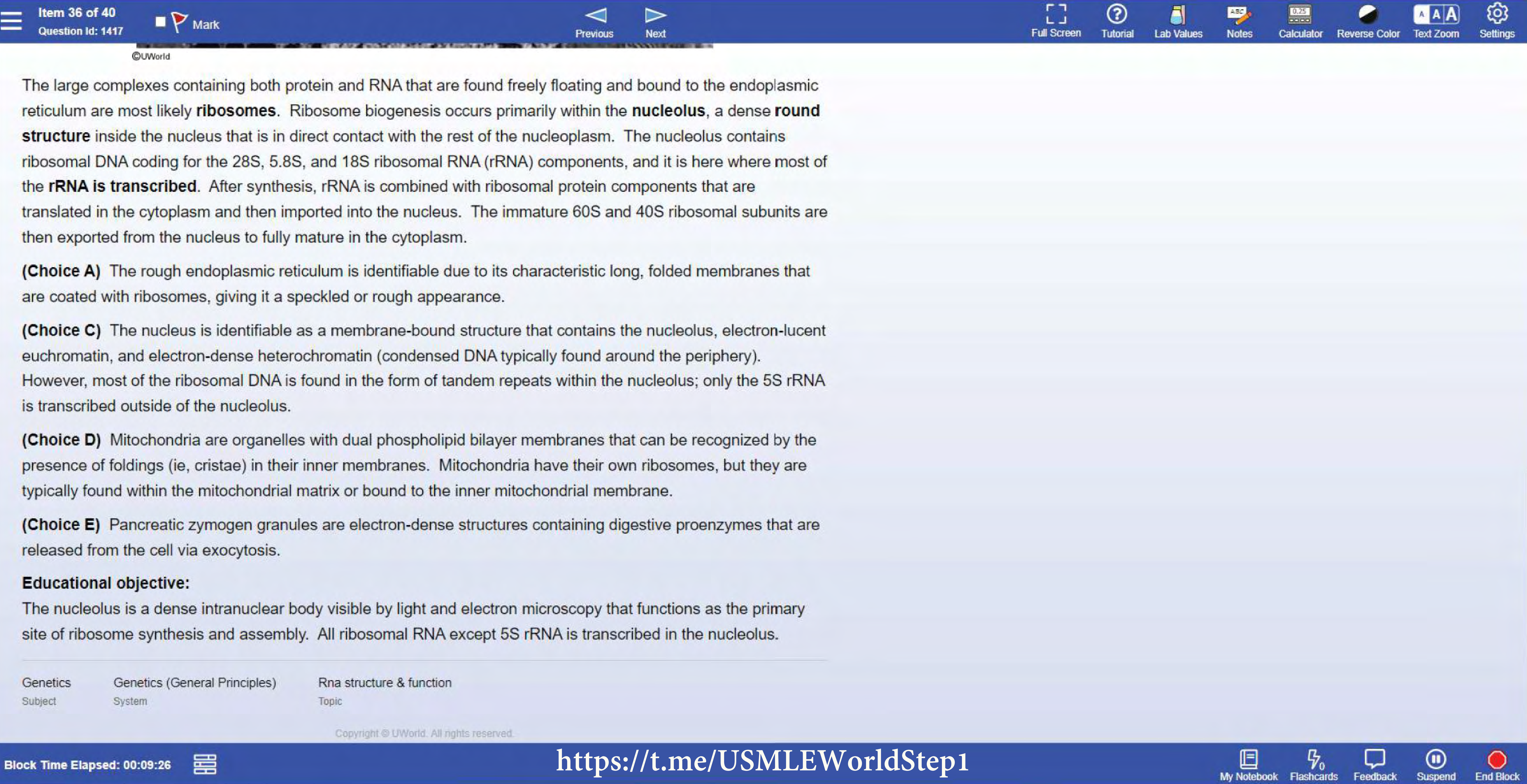
○ B. CCA
○ C. Methylguanosine triphosphate
○ D. Poly-A
○ E. TATA
○ F. UAG



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The large complexes containing both protein and RNA that are found freely floating and bound to the endoplasmic reticulum are most likely **ribosomes**. Ribosome biogenesis occurs primarily within the **nucleolus**, a dense **round structure** inside the nucleus that is in direct contact with the rest of the nucleoplasm. The nucleolus contains ribosomal DNA coding for the 28S, 5.8S, and 18S ribosomal RNA (rRNA) components, and it is here where most of the **rRNA is transcribed**. After synthesis, rRNA is combined with ribosomal protein components that are translated in the cytoplasm and then imported into the nucleus. The immature 60S and 40S ribosomal subunits are then exported from the nucleus to fully mature in the cytoplasm.

(Choice A) The rough endoplasmic reticulum is identifiable due to its characteristic long, folded membranes that are coated with ribosomes, giving it a speckled or rough appearance.

(Choice C) The nucleus is identifiable as a membrane-bound structure that contains the nucleolus, electron-lucent euchromatin, and electron-dense heterochromatin (condensed DNA typically found around the periphery). However, most of the ribosomal DNA is found in the form of tandem repeats within the nucleolus; only the 5S rRNA is transcribed outside of the nucleolus.

(Choice D) Mitochondria are organelles with dual phospholipid bilayer membranes that can be recognized by the presence of foldings (ie, cristae) in their inner membranes. Mitochondria have their own ribosomes, but they are typically found within the mitochondrial matrix or bound to the inner mitochondrial membrane.

(Choice E) Pancreatic zymogen granules are electron-dense structures containing digestive proenzymes that are released from the cell via exocytosis.

Educational objective:

The nucleolus is a dense intranuclear body visible by light and electron microscopy that functions as the primary site of ribosome synthesis and assembly. All ribosomal RNA except 5S rRNA is transcribed in the nucleolus.

Genetics	Genetics (General Principles)	Rna structure & function
Subject	System	Topic

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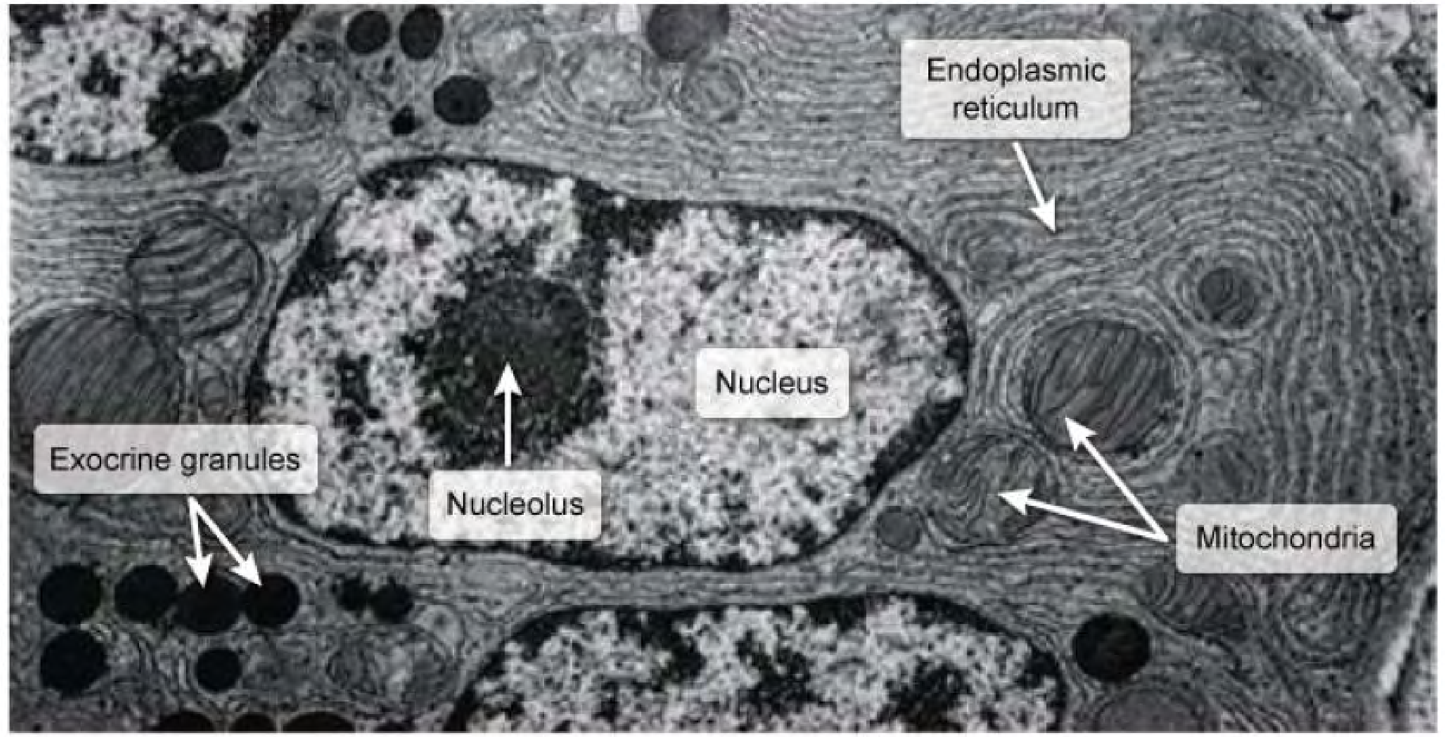
Cellular organelles under electron microscopy

Exhibit Display

Cellular organelles under electron microscopy



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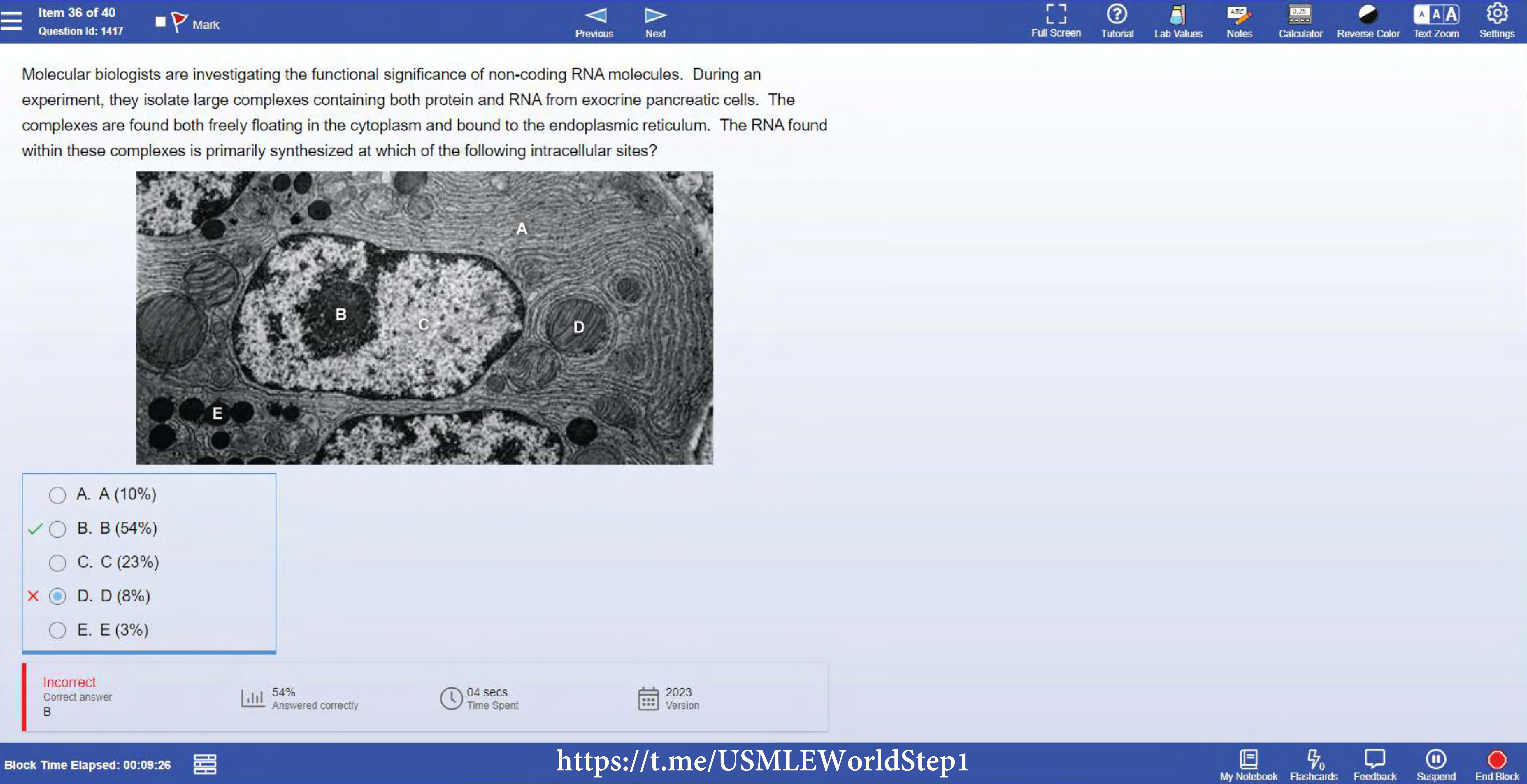
(Choice C) The nucleus is identifiable as a membrane-bound structure that contains the nucleolus, electron-lucent euchromatin, and electron-dense heterochromatin (condensed DNA typically found around the periphery). However, most of the ribosomal DNA is found in the form of tandem repeats within the nucleolus; only the 5S rRNA is transcribed outside of the nucleolus.


Item 36 of 40
Question Id: 1417
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Molecular biologists are investigating the functional significance of non-coding RNA molecules. During an experiment, they isolate large complexes containing both protein and RNA from exocrine pancreatic cells. The complexes are found both freely floating in the cytoplasm and bound to the endoplasmic reticulum. The RNA found within these complexes is primarily synthesized at which of the following intracellular sites?

- ○ A. A (10%)
- ✓ ○ B. B (54%)
- ○ C. C (23%)
- ✗ ● D. D (8%)
- ○ E. E (3%)

Incorrect
Correct answer
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54%
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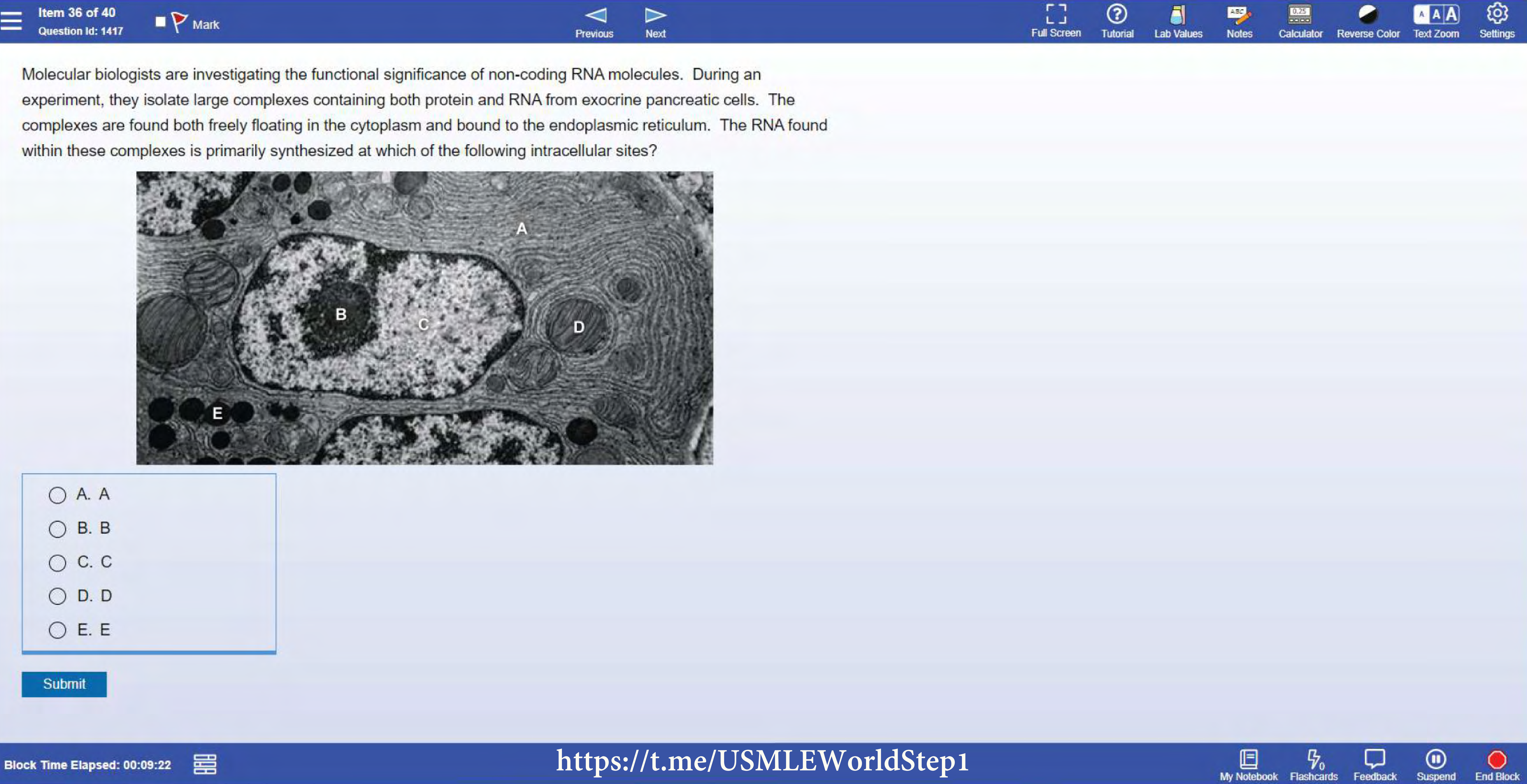
Item 36 of 40
Question Id: 1417
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
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Molecular biologists are investigating the functional significance of non-coding RNA molecules. During an experiment, they isolate large complexes containing both protein and RNA from exocrine pancreatic cells. The complexes are found both freely floating in the cytoplasm and bound to the endoplasmic reticulum. The RNA found within these complexes is primarily synthesized at which of the following intracellular sites?

○ A. A
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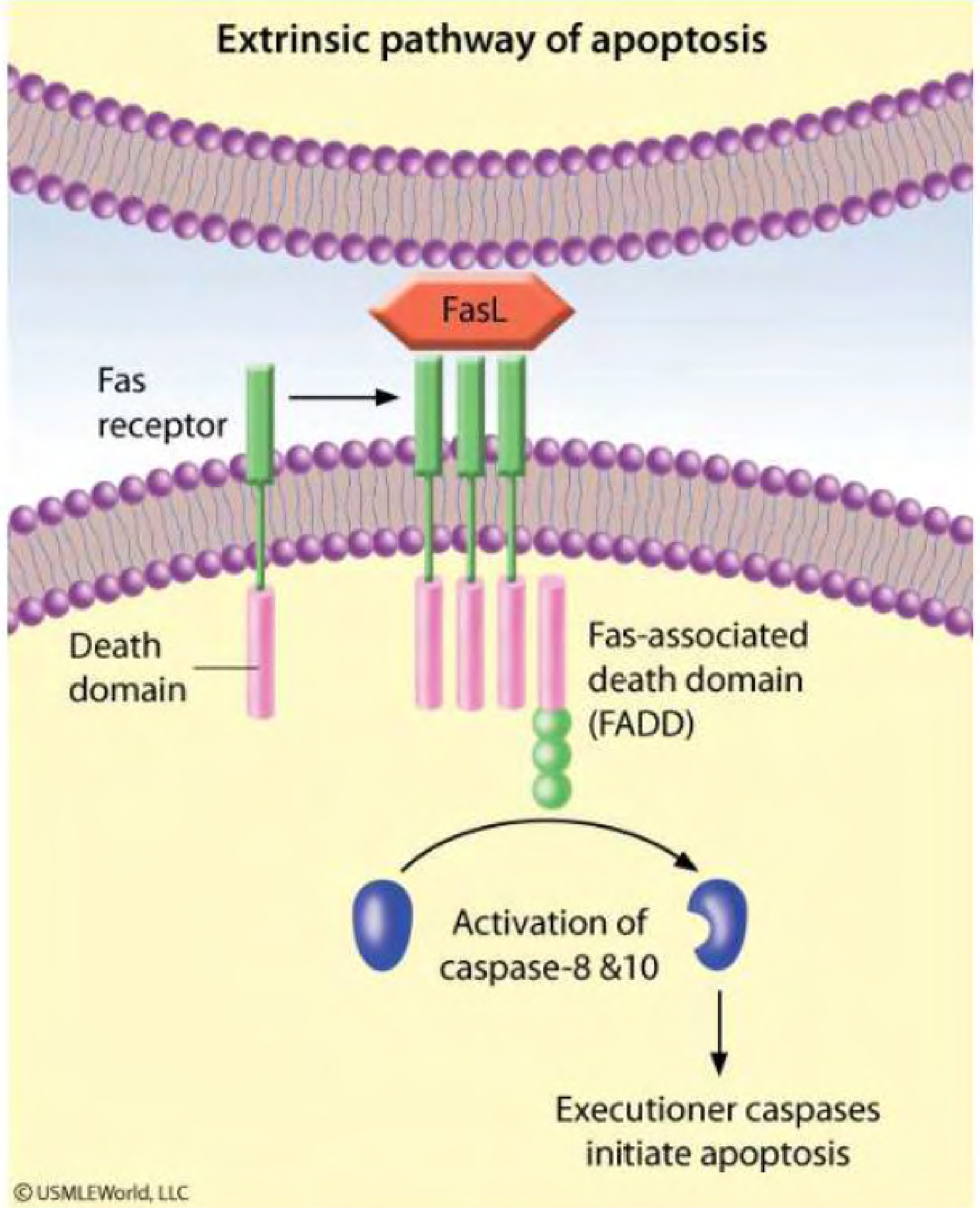
Extrinsic pathway of apoptosis
FasL
Fas receptor
Death domain
Fas-associated death domain (FADD)
Activation of caspase-8 &10
Executioner caspases initiate apoptosis
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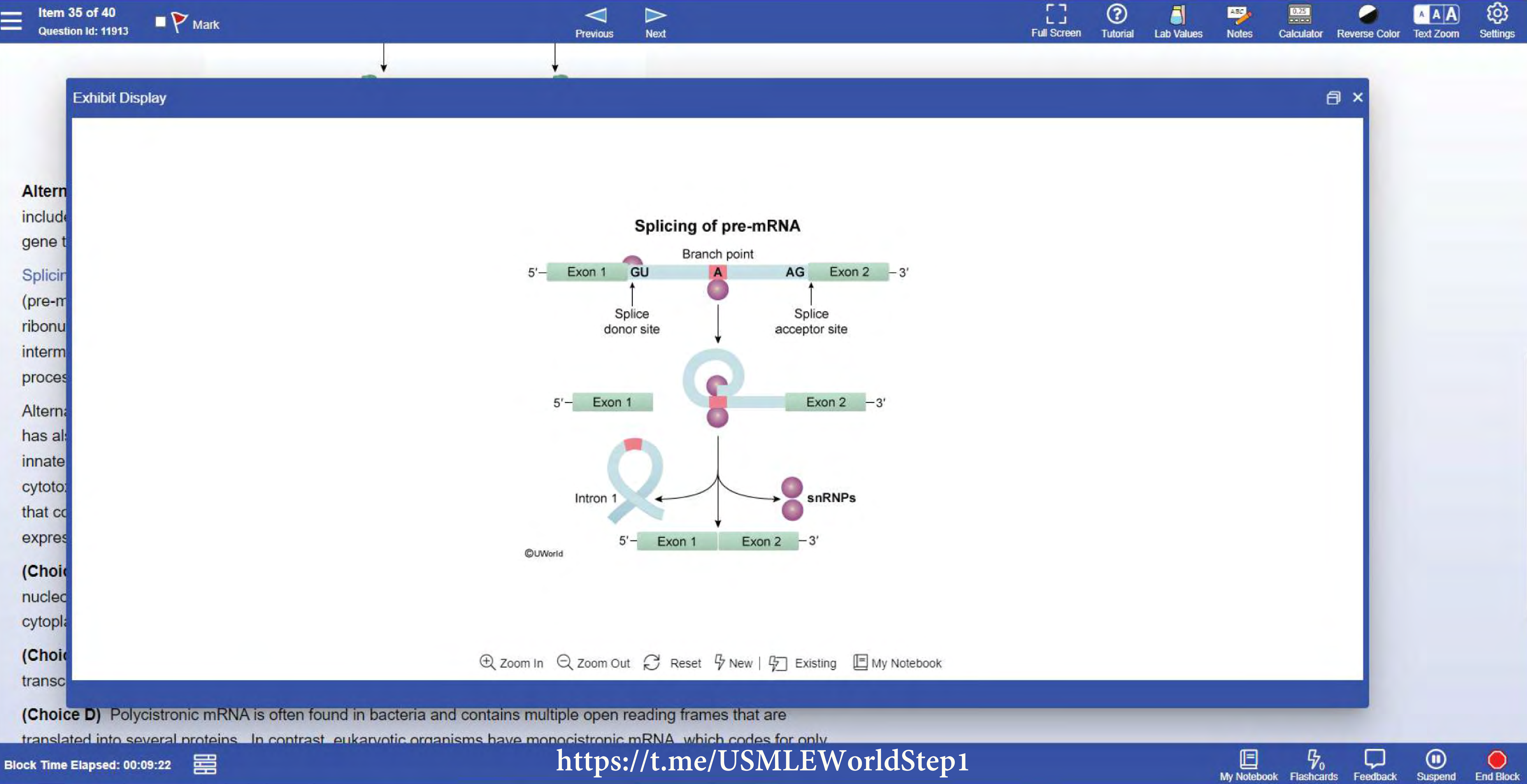
(Choice D) Polycistronic mRNA is often found in bacteria and contains multiple open reading frames that are translated into several proteins. In contrast, eukaryotic organisms have monocistronic mRNA, which codes for only


Item 35 of 40
Question Id: 11913
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
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Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Splicing of pre-mRNA
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Exon 2
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My Notebook
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My Notebook
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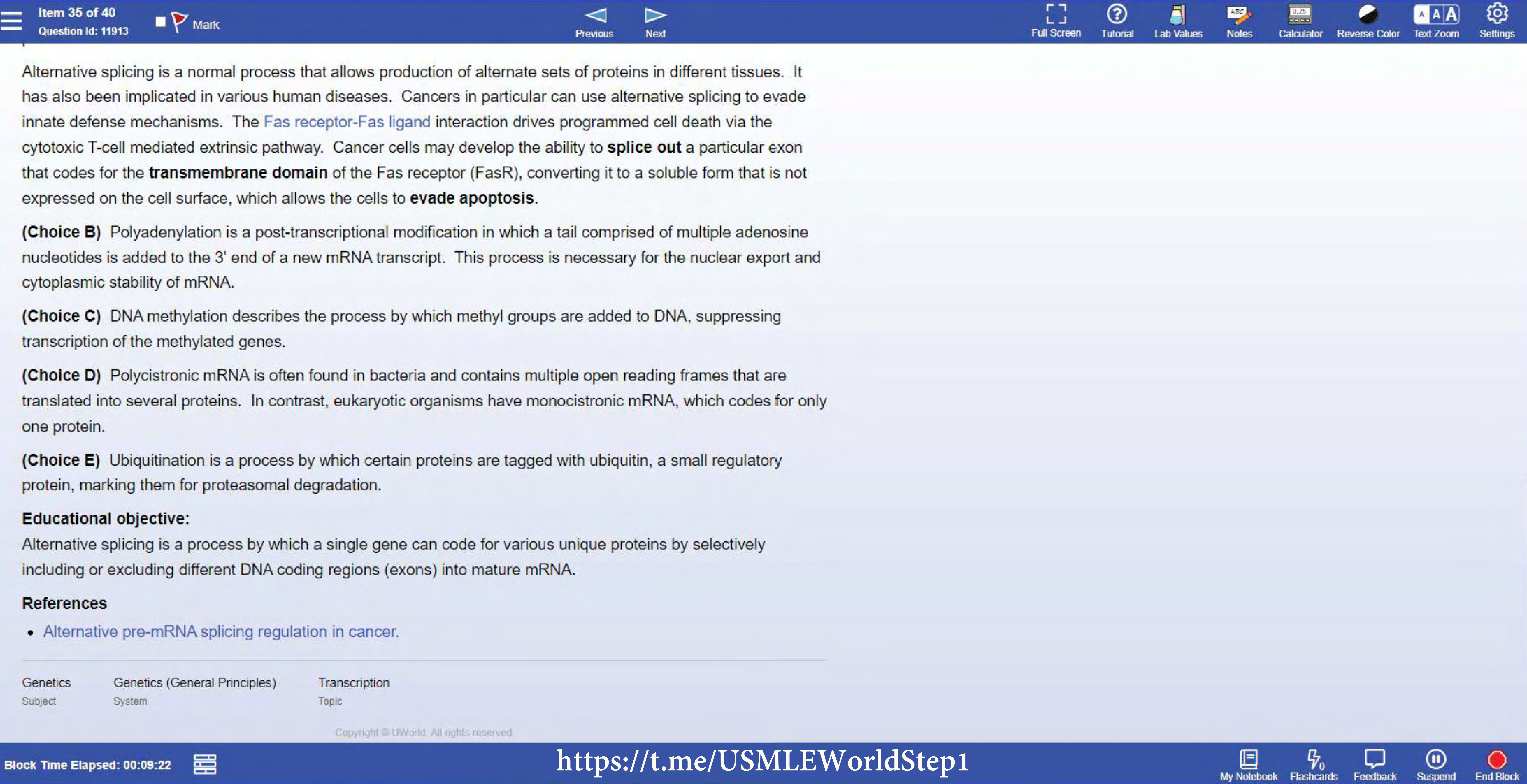
Item 35 of 40
Question Id: 11913
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Alternative splicing is a normal process that allows production of alternate sets of proteins in different tissues. It has also been implicated in various human diseases. Cancers in particular can use alternative splicing to evade innate defense mechanisms. The Fas receptor-Fas ligand interaction drives programmed cell death via the cytotoxic T-cell mediated extrinsic pathway. Cancer cells may develop the ability to **splice out** a particular exon that codes for the **transmembrane domain** of the Fas receptor (FasR), converting it to a soluble form that is not expressed on the cell surface, which allows the cells to **evade apoptosis**.

(Choice B) Polyadenylation is a post-transcriptional modification in which a tail comprised of multiple adenosine nucleotides is added to the 3' end of a new mRNA transcript. This process is necessary for the nuclear export and cytoplasmic stability of mRNA.

(Choice C) DNA methylation describes the process by which methyl groups are added to DNA, suppressing transcription of the methylated genes.

(Choice D) Polycistronic mRNA is often found in bacteria and contains multiple open reading frames that are translated into several proteins. In contrast, eukaryotic organisms have monocistronic mRNA, which codes for only one protein.

(Choice E) Ubiquitination is a process by which certain proteins are tagged with ubiquitin, a small regulatory protein, marking them for proteasomal degradation.

Educational objective:

Alternative splicing is a process by which a single gene can code for various unique proteins by selectively including or excluding different DNA coding regions (exons) into mature mRNA.

References

- Alternative pre-mRNA splicing regulation in cancer.

Genetics	Genetics (General Principles)	Transcription
Subject	System	Topic

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Flashcards
Feedback
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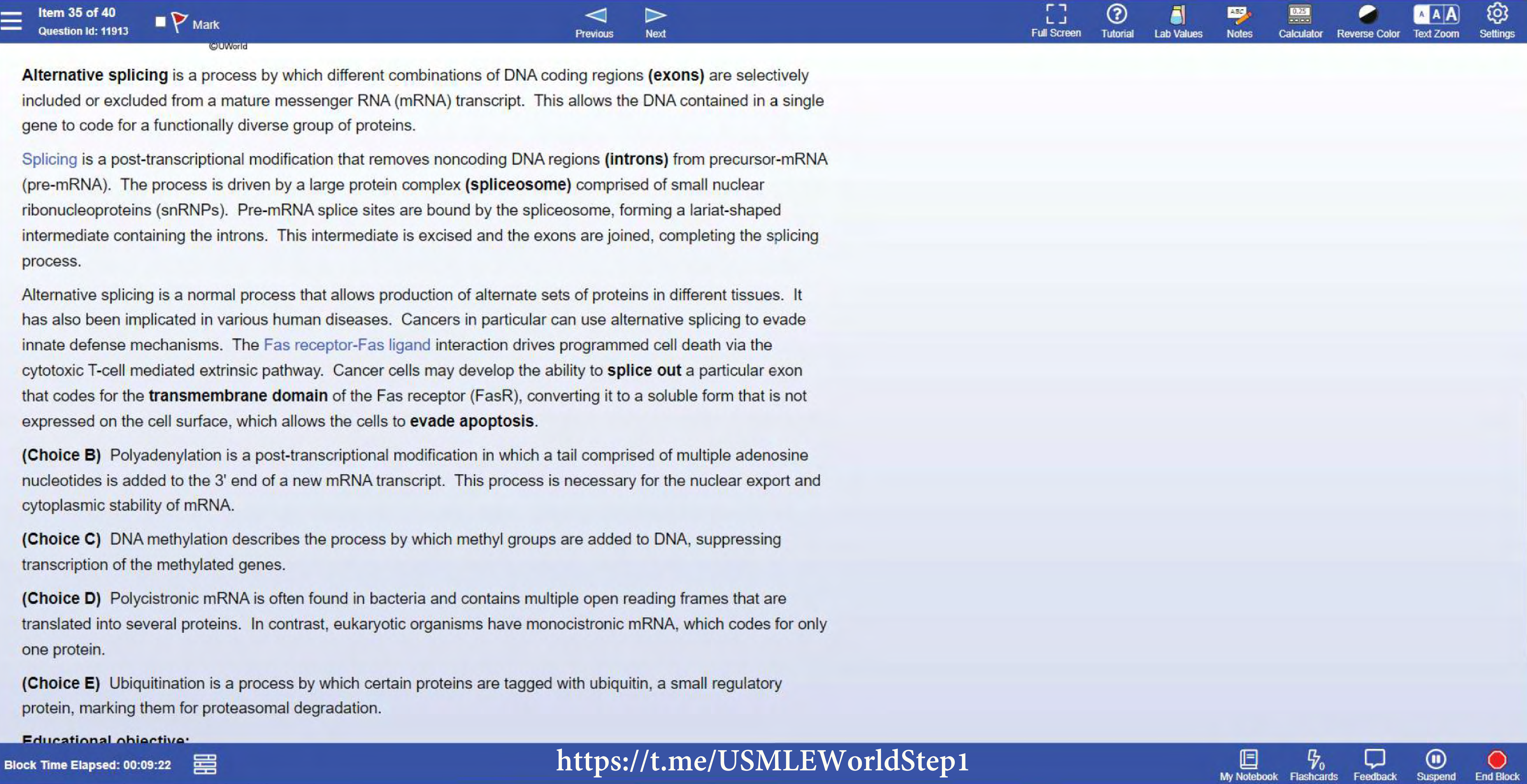

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Alternative splicing is a process by which different combinations of DNA coding regions **(exons)** are selectively included or excluded from a mature messenger RNA (mRNA) transcript. This allows the DNA contained in a single gene to code for a functionally diverse group of proteins.

Splicing is a post-transcriptional modification that removes noncoding DNA regions **(introns)** from precursor-mRNA (pre-mRNA). The process is driven by a large protein complex **(spliceosome)** comprised of small nuclear ribonucleoproteins (snRNPs). Pre-mRNA splice sites are bound by the spliceosome, forming a lariat-shaped intermediate containing the introns. This intermediate is excised and the exons are joined, completing the splicing process.

Alternative splicing is a normal process that allows production of alternate sets of proteins in different tissues. It has also been implicated in various human diseases. Cancers in particular can use alternative splicing to evade innate defense mechanisms. The Fas receptor-Fas ligand interaction drives programmed cell death via the cytotoxic T-cell mediated extrinsic pathway. Cancer cells may develop the ability to **splice out** a particular exon that codes for the **transmembrane domain** of the Fas receptor (FasR), converting it to a soluble form that is not expressed on the cell surface, which allows the cells to **evade apoptosis**.

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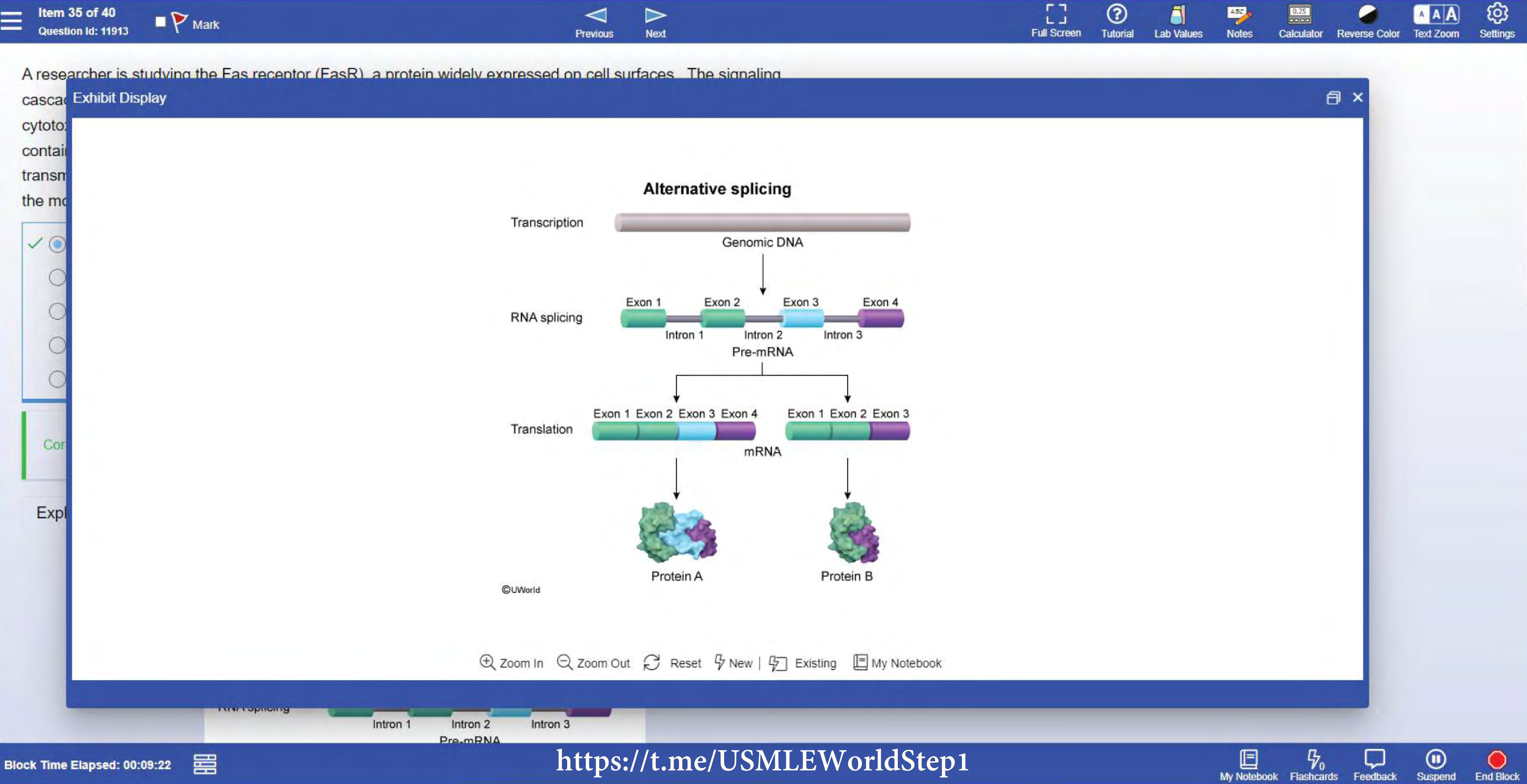
Educational objective:



Item 35 of 40
Question Id: 11913
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A researcher is studying the Fas receptor (FasR), a protein widely expressed on cell surfaces. The signaling

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Alternative splicing

Transcription
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Exon 1
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Zoom In
Zoom Out
Reset
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My Notebook
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My Notebook
Flashcards
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Suspend
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A researcher is studying the Fas receptor (FasR), a protein widely expressed on cell surfaces. The signaling cascade of programmed cell death is initiated when FasR binds to its ligand (FasL), which is expressed on cytotoxic T cells. In an experiment, cancer cells that escaped elimination by the immune system were found to contain soluble Fas proteins that did not promote apoptosis. The soluble Fas proteins were shorter and lacked the transmembrane domain. DNA analysis of these cells revealed no *FAS* gene mutations. Which of the following is the most likely explanation for the formation of altered Fas proteins in these cancer cells?

- ✓ ● A. Alternative splicing (70%)
- ○ B. Defective polyadenylation (7%)
- ○ C. DNA methylation (11%)
- ○ D. Polycistronic mRNA (3%)
- ○ E. Protein ubiquitination (8%)

Correct

70%
Answered correctly

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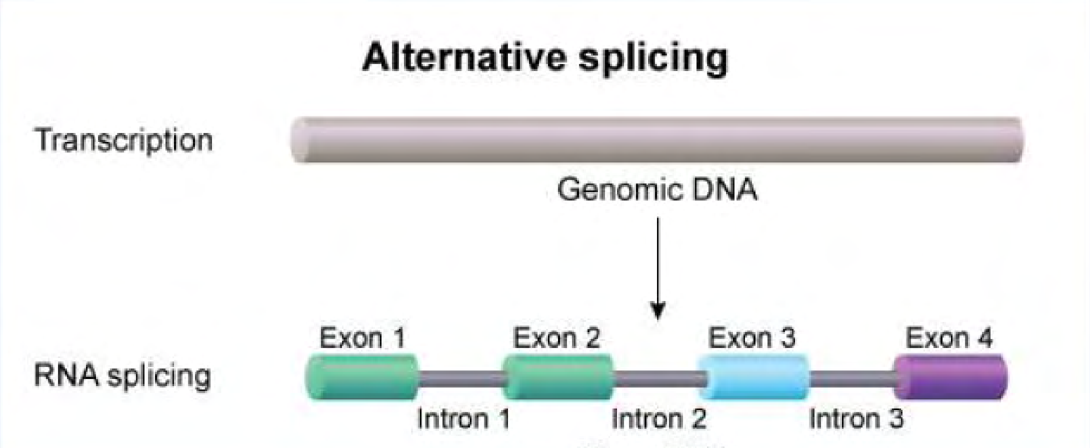
Explanation


Alternative splicing
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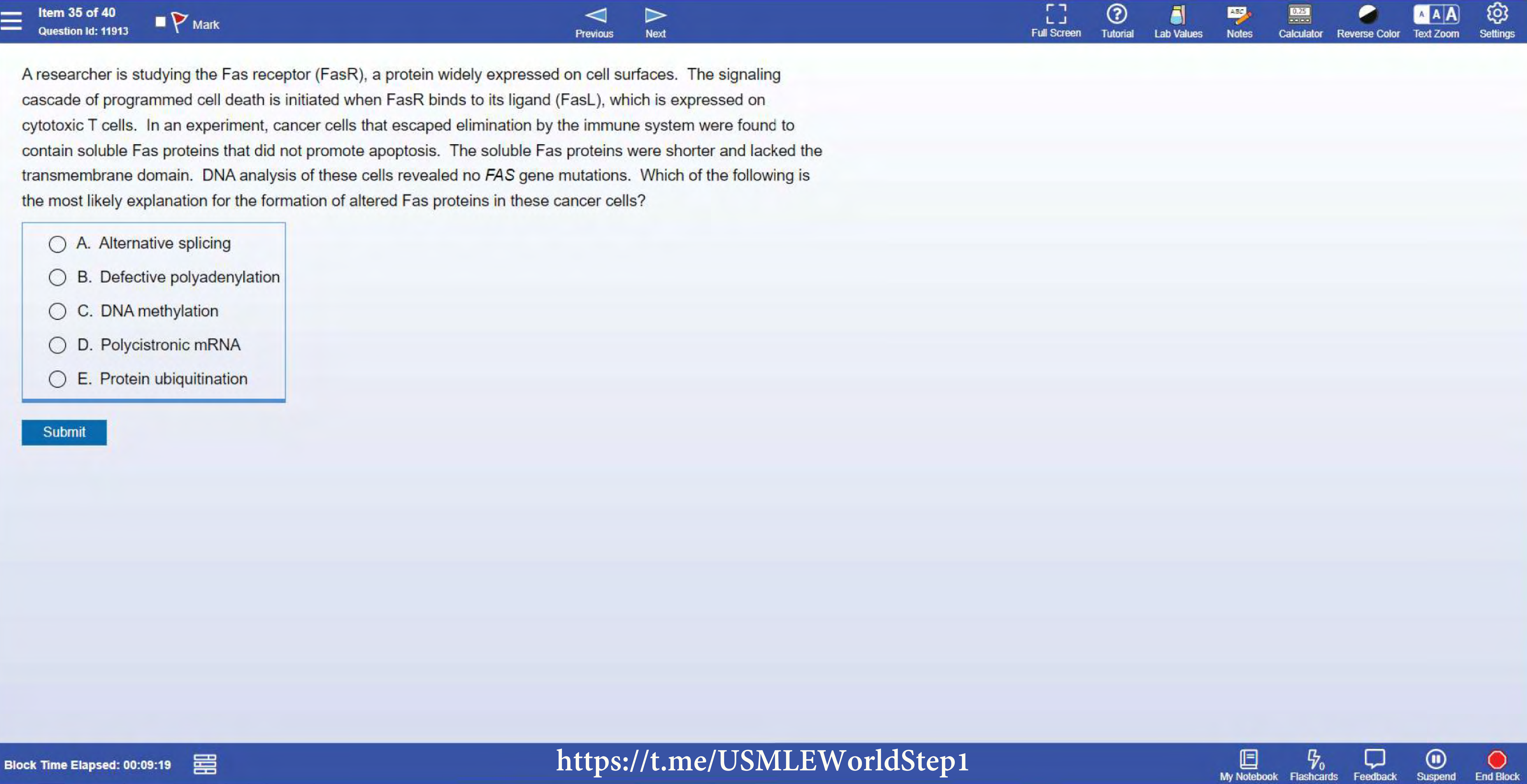
Item 35 of 40
Question Id: 11913
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ A. Alternative splicing
- ○ B. Defective polyadenylation
- ○ C. DNA methylation
- ○ D. Polycistronic mRNA
- ○ E. Protein ubiquitination

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Flashcards
Feedback
Suspend
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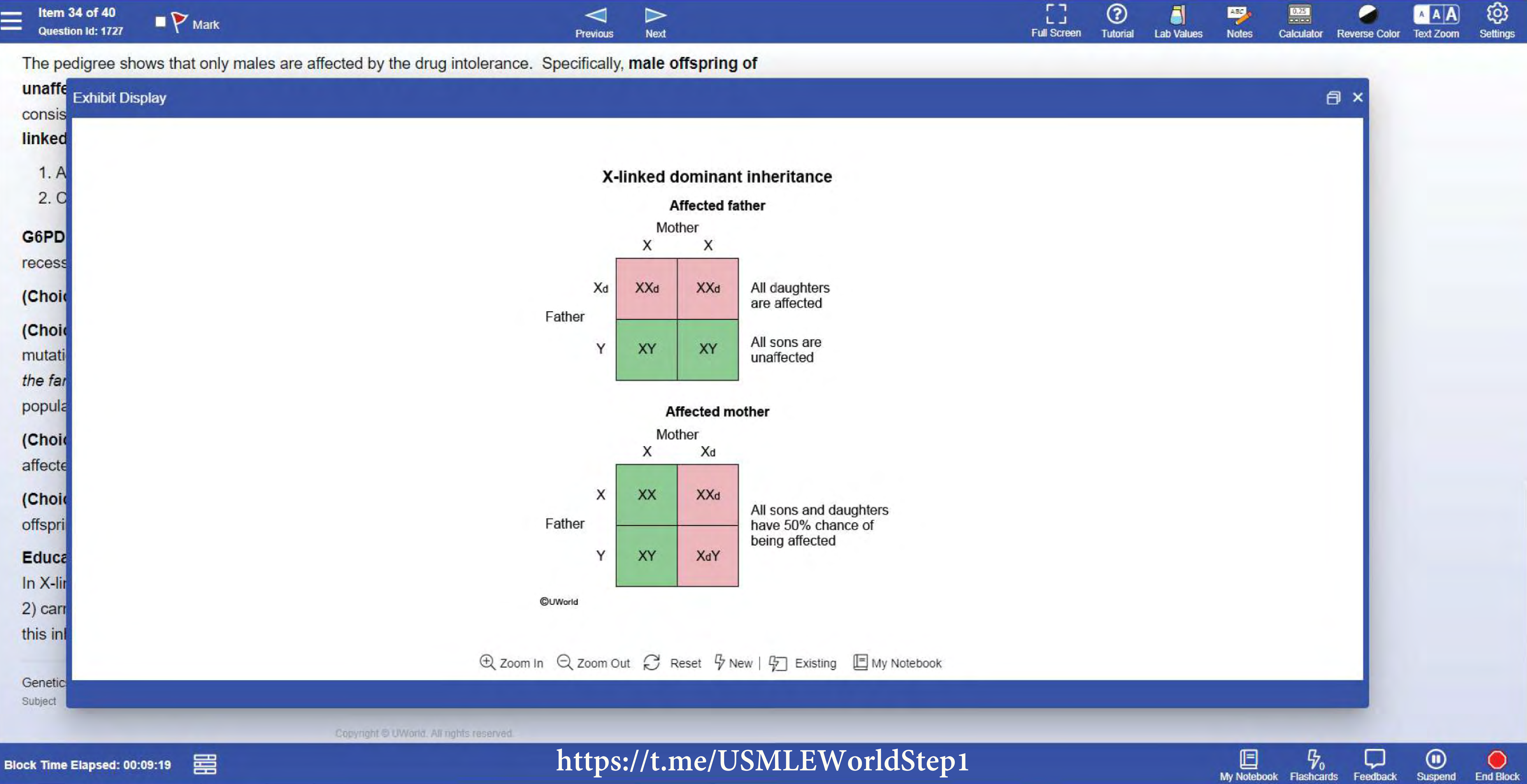
Item 34 of 40
Question Id: 1727
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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The pedigree shows that only males are affected by the drug intolerance. Specifically, **male offspring of**
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X-linked dominant inheritance

Affected father

Father \ Mother	X	X
X_d	XX_d 🟥	XX_d 🟥
Y	XY 🟩	XY 🟩

All daughters are affected

All sons are unaffected

Affected mother

Father \ Mother	X	X_d
X	XX 🟩	XX_d 🟥
Y	XY 🟩	X_dY 🟥

All sons and daughters have 50% chance of being affected

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Reset
New
Existing
My Notebook

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Block Time Elapsed: 00:09:19

My Notebook
Flashcards
Feedback
Suspend
End Block

Item 34 of 40
Question Id: 1727
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

The pedigree shows that only males are affected by the drug intolerance. Specifically, **male offspring of unaffected parents** are affected. There is no evidence of male-to-male transmission. This pattern is most consistent with X-linked recessive inheritance from an asymptomatic carrier female in the first generation. In **X-linked recessive inheritance**:

1. Affected males will always produce unaffected sons and carrier daughters.
2. Carrier females have a 50% chance of producing an affected son or carrier daughter.

G6PD deficiency, which causes acute hemolytic anemia on exposure to oxidant drugs, follows an X-linked recessive pattern of inheritance.

(Choice A) With autosomal dominant inheritance, affected individuals have at least 1 parent that is also affected.

(Choice B) In autosomal recessive inheritance, both parents must at least be carriers (heterozygous) for the mutation in order to produce affected offspring. However, the father of the marked individual comes from *outside the family* and would be unlikely to carry the mutation (the question states the mutation is rare in the general population).

(Choice C) In X-linked dominant inheritance, affected individuals have at least 1 parent (of either sex) that is also affected. An affected male will always produce affected daughters, but none of his sons will be affected.

(Choice E) Conditions with mitochondrial inheritance are transmitted only by females. All of an affected female's offspring are likely to show signs of the disease.

Educational objective:

In X-linked recessive inheritance 1) affected males will always produce *unaffected* sons and *carrier* daughters, and 2) carrier females have a 50% chance of producing *affected* sons and *carrier* daughters. G6PD deficiency follows this inheritance pattern and causes acute hemolytic anemia in response to oxidant drugs.

Genetics	Genetics (General Principles)	Genetic inheritance
Subject	System	Topic

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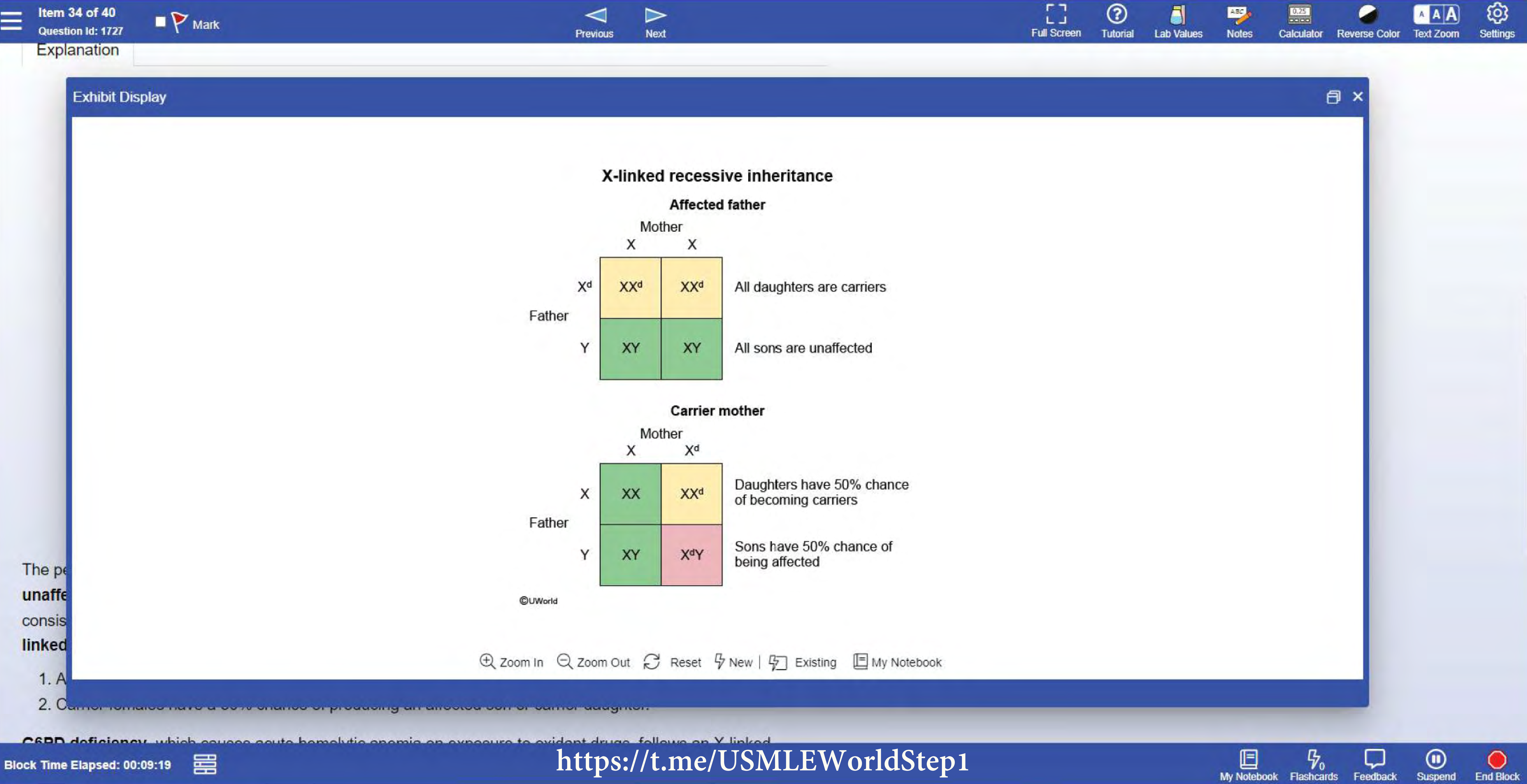
Item 34 of 40
Question Id: 1727
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:09:19
My Notebook
Flashcards
Feedback
Suspend
End Block

X-linked recessive inheritance

Affected father

Father \ Mother	X	X	
X^d	XX^d	XX^d	All daughters are carriers
Y	XY	XY	All sons are unaffected

Carrier mother

Father \ Mother	X	X^d	
X	XX	XX^d	Daughters have 50% chance of becoming carriers
Y	XY	X^dY	Sons have 50% chance of being affected

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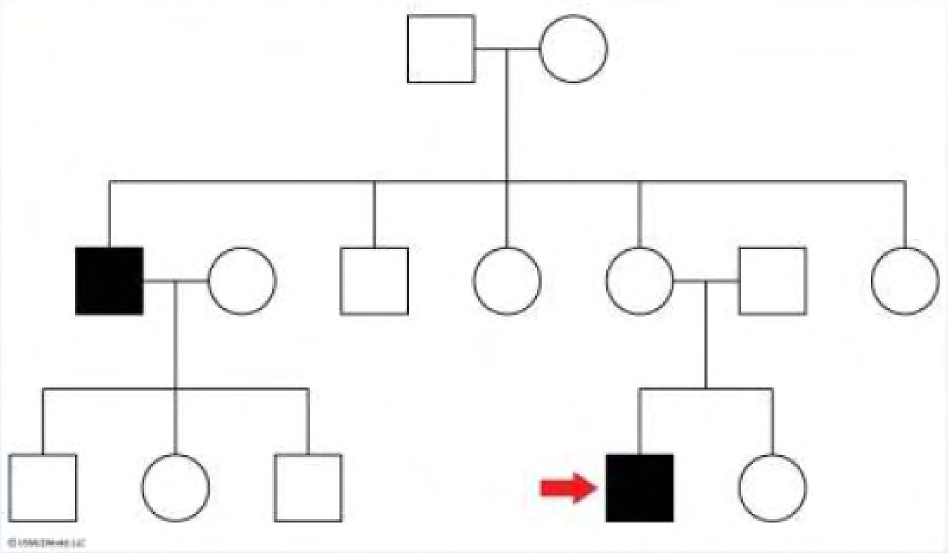
1. A
2. Carrier females have a 50% chance of producing an affected son or carrier daughter.

G6PD deficiency, which causes acute hemolytic anemia on exposure to oxidant drugs, follows an X-linked

A 25-year-old man experiences severe intolerance to certain medications. On 2 occasions, his reactions to various drugs have necessitated hospital admission. His family pedigree with respect to this condition is shown below, with the red arrow indicating his position within the family.



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

- ✗ ● A. Autosomal dominant (1%)
- ○ B. Autosomal recessive (15%)
- ○ C. X-linked dominant (4%)
- ✓ ○ D. X-linked recessive (75%)
- ○ E. Mitochondrial (3%)

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Correct answer
D

75%
Answered correctly

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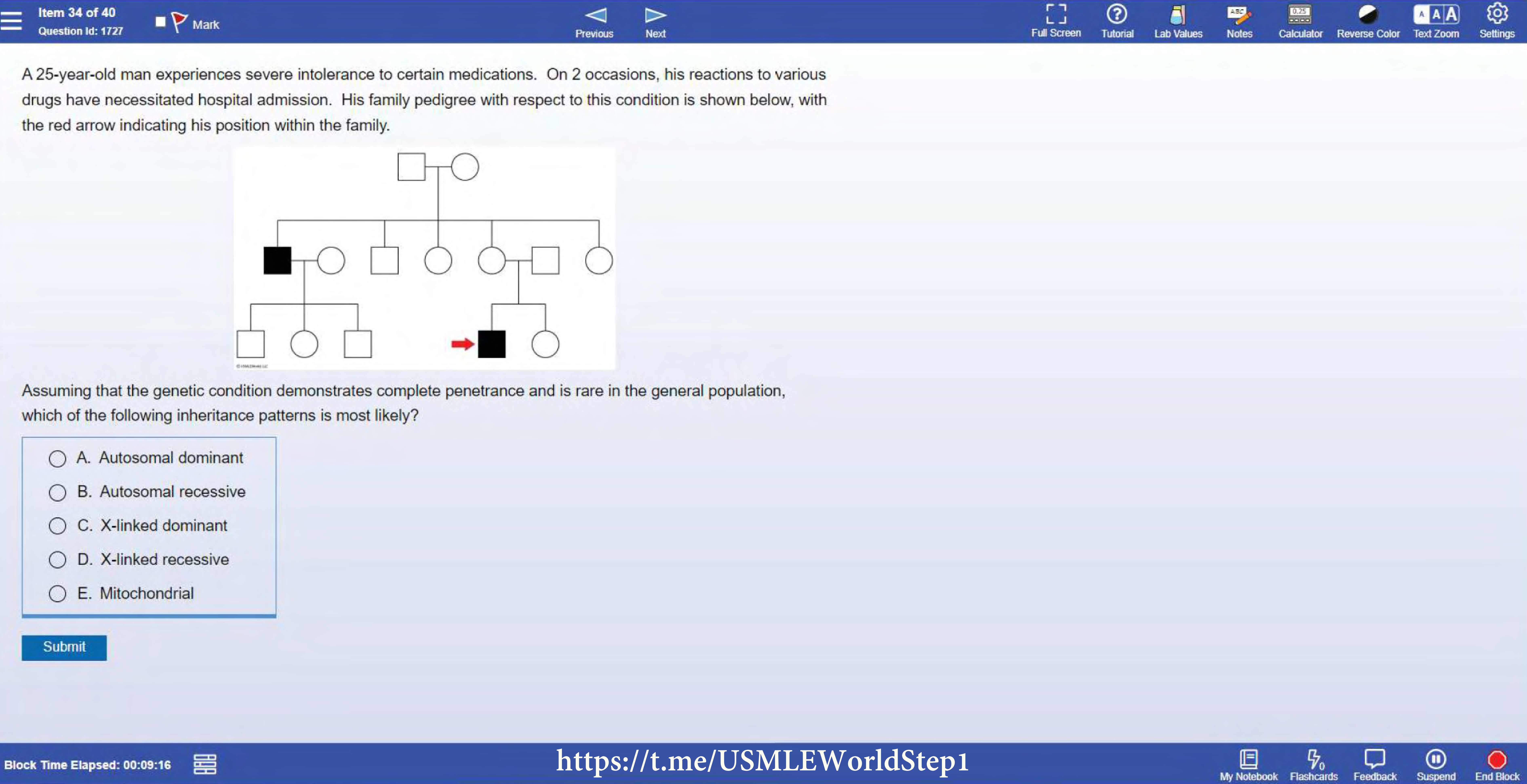
Item 34 of 40
Question Id: 1727
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Autosomal dominant
○ B. Autosomal recessive
○ C. X-linked dominant
○ D. X-linked recessive
○ E. Mitochondrial

Submit
Block Time Elapsed: 00:09:16
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 34 of 40
Question Id: 1727
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:09:13
My Notebook
Flashcards
Feedback
Suspend
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○ A. Autosomal dominant
○ B. Autosomal recessive
○ C. X-linked dominant
○ D. X-linked recessive
○ E. Mitochondrial

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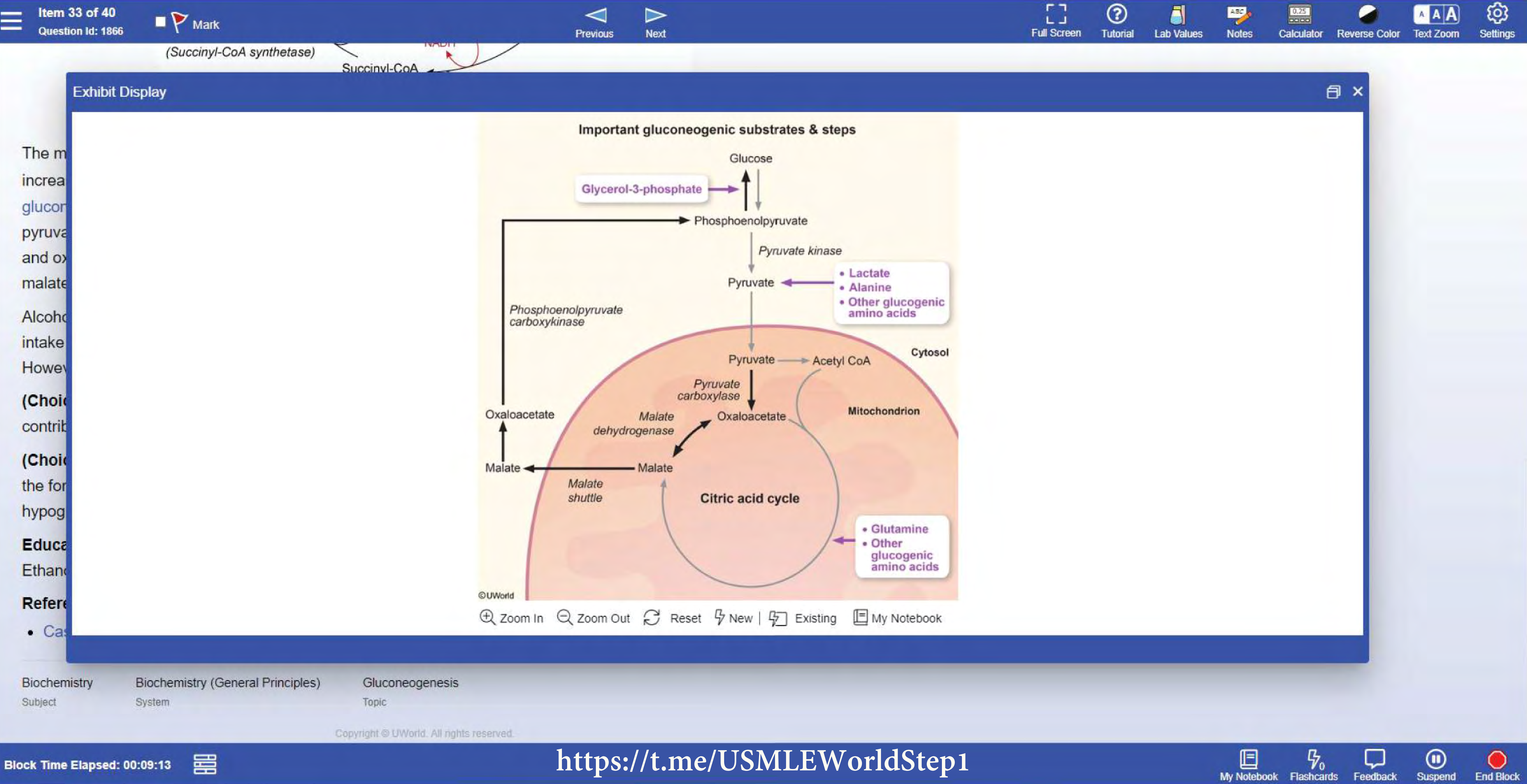
Item 33 of 40
Question Id: 1866
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Exhibit Display
Important gluconeogenic substrates & steps
Glucose
Glycerol-3-phosphate
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
• Lactate
• Alanine
• Other glucogenic amino acids
Phosphoenolpyruvate carboxykinase
Pyruvate
Acetyl CoA
Cytosol
Pyruvate carboxylase
Mitochondrion
Oxaloacetate
Malate dehydrogenase
Oxaloacetate
Malate
Malate
Malate shuttle
Citric acid cycle
• Glutamine
• Other glucogenic amino acids
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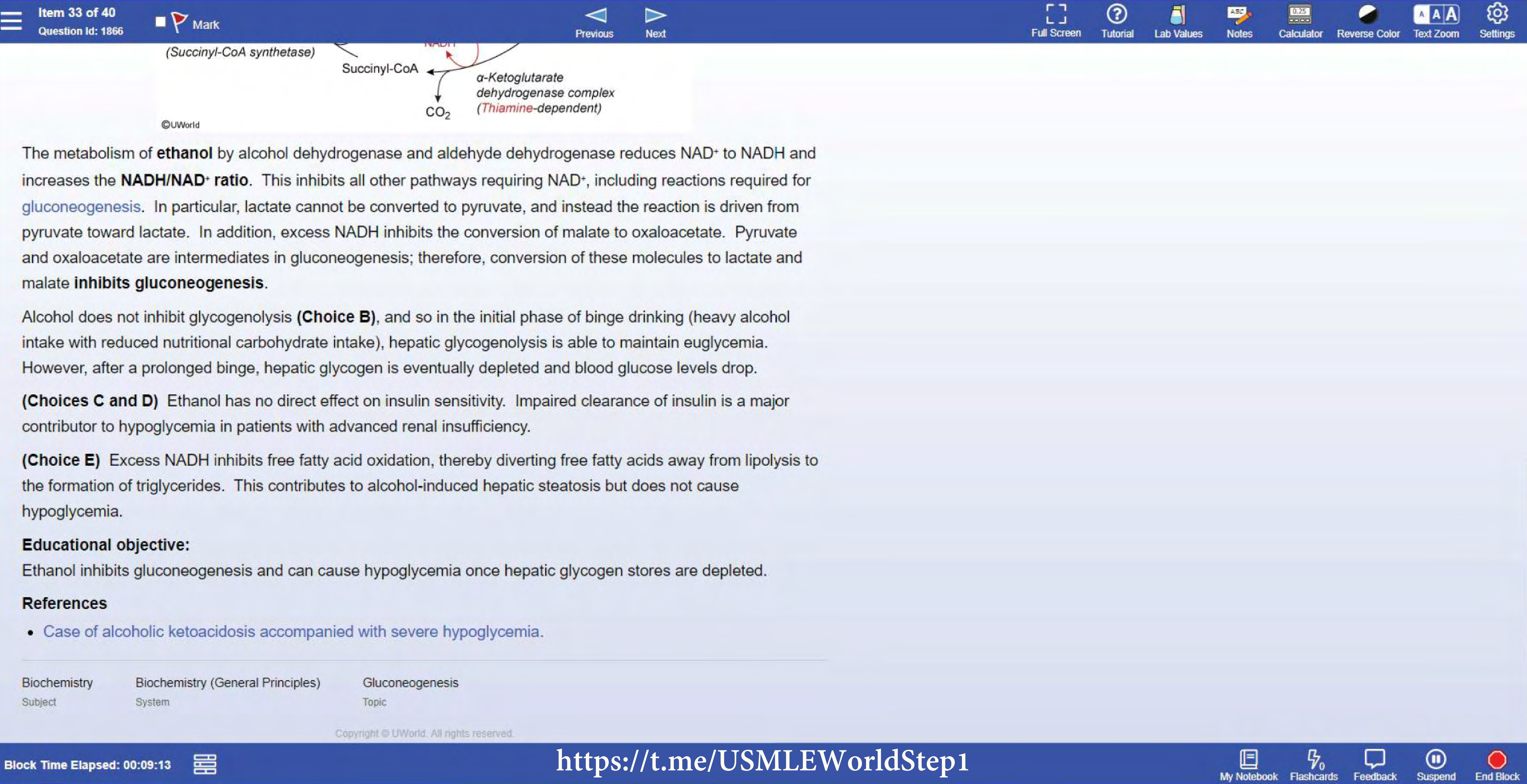
Item 33 of 40
Question Id: 1866
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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NADH
Succinyl-CoA
α-Ketoglutarate
dehydrogenase complex
(Thiamine-dependent)
CO2
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My Notebook
Flashcards
Feedback
Suspend
End Block

The metabolism of **ethanol** by alcohol dehydrogenase and aldehyde dehydrogenase reduces NAD^+ to NADH and increases the **NADH/NAD^+ ratio**. This inhibits all other pathways requiring NAD^+, including reactions required for gluconeogenesis. In particular, lactate cannot be converted to pyruvate, and instead the reaction is driven from pyruvate toward lactate. In addition, excess NADH inhibits the conversion of malate to oxaloacetate. Pyruvate and oxaloacetate are intermediates in gluconeogenesis; therefore, conversion of these molecules to lactate and malate **inhibits gluconeogenesis**.

Alcohol does not inhibit glycogenolysis **(Choice B)**, and so in the initial phase of binge drinking (heavy alcohol intake with reduced nutritional carbohydrate intake), hepatic glycogenolysis is able to maintain euglycemia. However, after a prolonged binge, hepatic glycogen is eventually depleted and blood glucose levels drop.

(Choices C and D) Ethanol has no direct effect on insulin sensitivity. Impaired clearance of insulin is a major contributor to hypoglycemia in patients with advanced renal insufficiency.

(Choice E) Excess NADH inhibits free fatty acid oxidation, thereby diverting free fatty acids away from lipolysis to the formation of triglycerides. This contributes to alcohol-induced hepatic steatosis but does not cause hypoglycemia.

Educational objective:

Ethanol inhibits gluconeogenesis and can cause hypoglycemia once hepatic glycogen stores are depleted.

References

- Case of alcoholic ketoacidosis accompanied with severe hypoglycemia.

Biochemistry	Biochemistry (General Principles)	Gluconeogenesis
Subject	System	Topic

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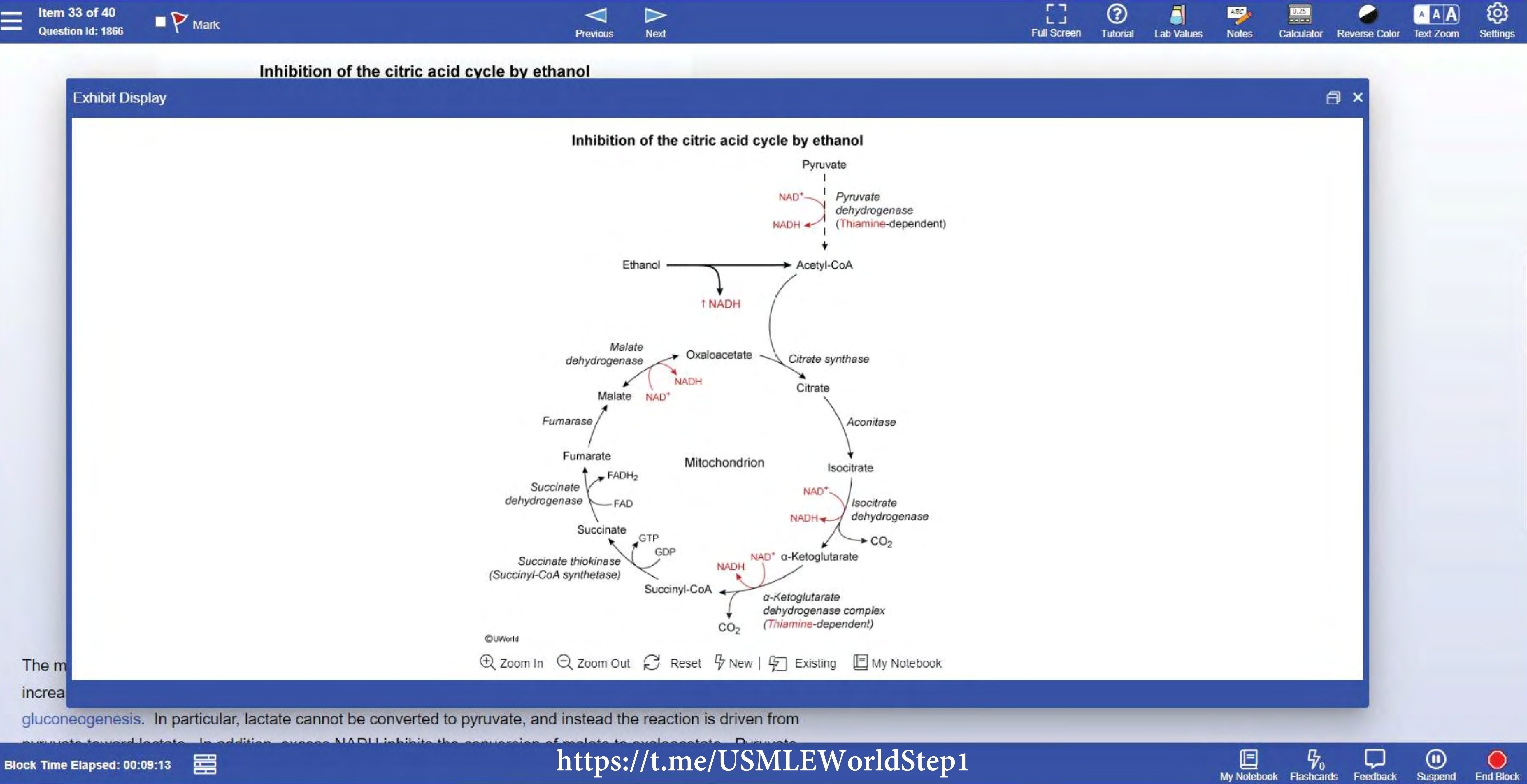
Item 33 of 40
Question Id: 1866
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:09:13
My Notebook
Flashcards
Feedback
Suspend
End Block

Inhibition of the citric acid cycle by ethanol

Inhibition of the citric acid cycle by ethanol

Pyruvate
NAD+
NADH
Pyruvate dehydrogenase (Thiamine-dependent)
Ethanol
Acetyl-CoA
↑ NADH
Malate dehydrogenase
Oxaloacetate
Citrate synthase
NADH
NAD+
Malate
Citrate
Fumarase
Aconitase
Fumarate
Mitochondrion
Isocitrate
FADH2
Succinate dehydrogenase
FAD
NAD+
Isocitrate dehydrogenase
NADH
Succinate
CO2
GTP
GDP
Succinate thiokinase (Succinyl-CoA synthetase)
NAD+
α-Ketoglutarate
NADH
Succinyl-CoA
α-Ketoglutarate dehydrogenase complex (Thiamine-dependent)
CO2
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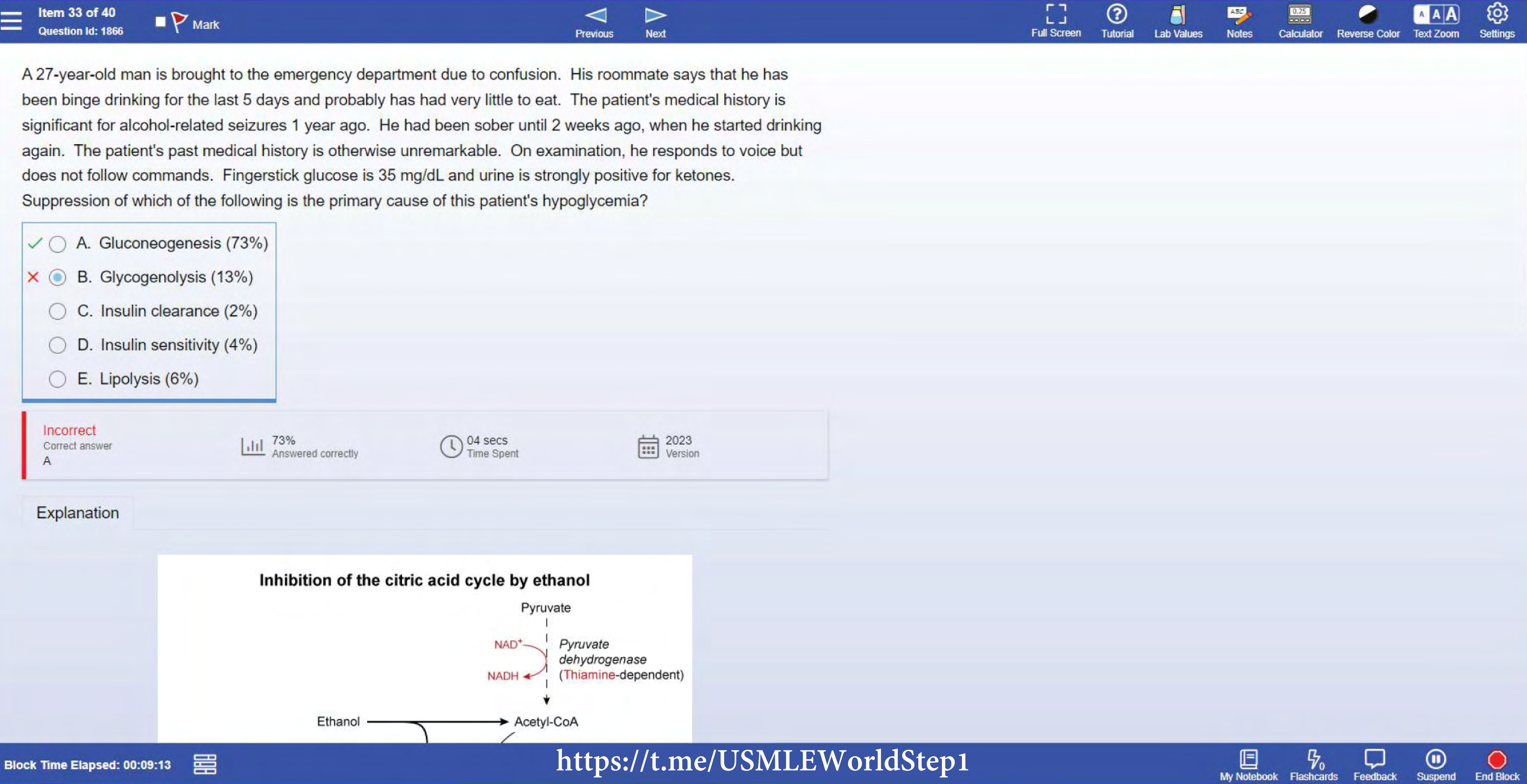
gluconeogenesis. In particular, lactate cannot be converted to pyruvate, and instead the reaction is driven from

pyruvate toward lactate. In addition, excess NADH inhibits the conversion of malate to oxaloacetate. Pyruvate


Item 33 of 40
Question Id: 1866
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 27-year-old man is brought to the emergency department due to confusion. His roommate says that he has been binge drinking for the last 5 days and probably has had very little to eat. The patient's medical history is significant for alcohol-related seizures 1 year ago. He had been sober until 2 weeks ago, when he started drinking again. The patient's past medical history is otherwise unremarkable. On examination, he responds to voice but does not follow commands. Fingerstick glucose is 35 mg/dL and urine is strongly positive for ketones. Suppression of which of the following is the primary cause of this patient's hypoglycemia?

✓ ○ A. Gluconeogenesis (73%)
✗ ● B. Glycogenolysis (13%)
○ C. Insulin clearance (2%)
○ D. Insulin sensitivity (4%)
○ E. Lipolysis (6%)

Incorrect
Correct answer
A

73%
Answered correctly

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Explanation

Inhibition of the citric acid cycle by ethanol

Pyruvate
NAD+
NADH
Pyruvate dehydrogenase (Thiamine-dependent)
Ethanol
Acetyl-CoA

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My Notebook
Flashcards
Feedback
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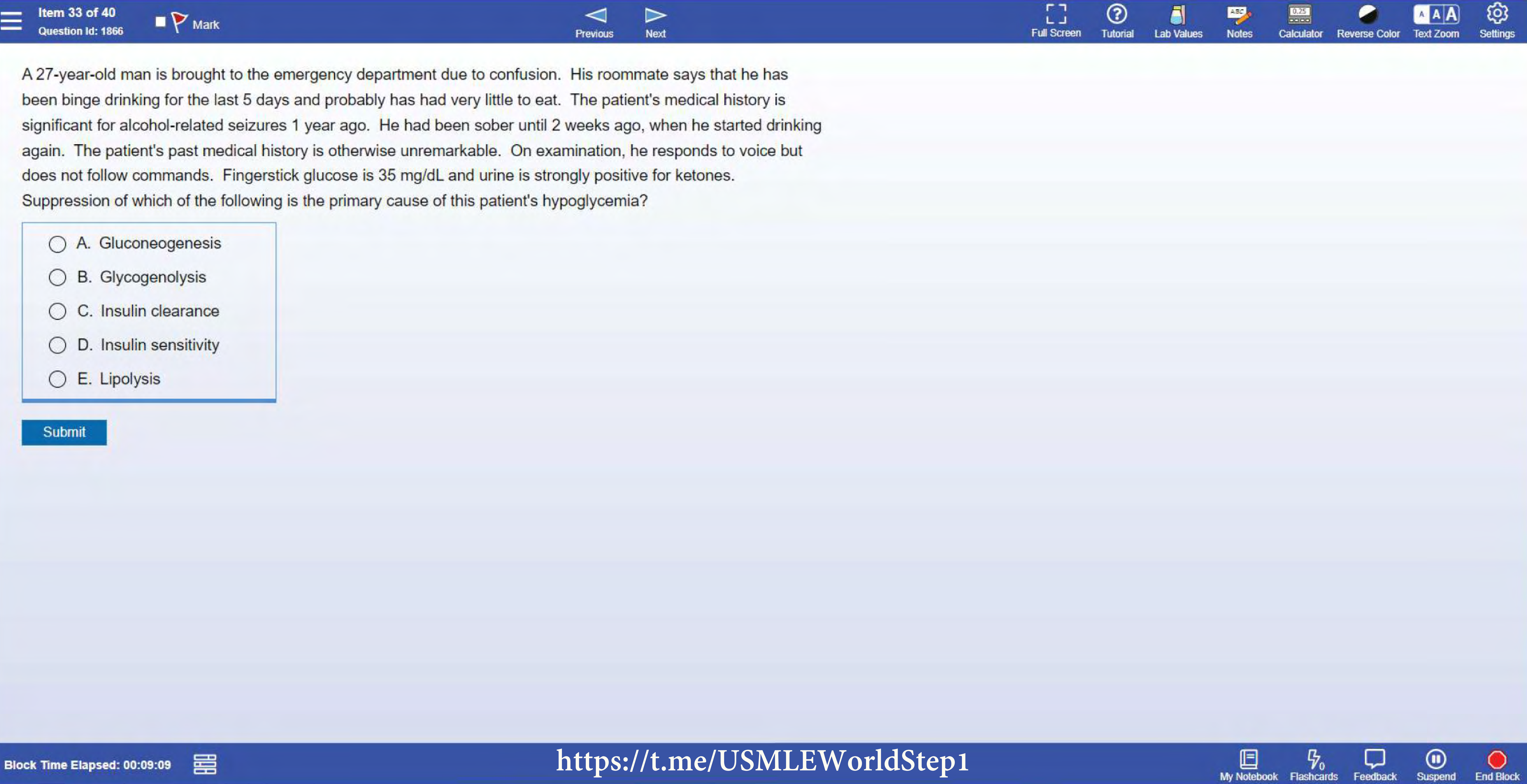
Item 33 of 40
Question Id: 1866
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 27-year-old man is brought to the emergency department due to confusion. His roommate says that he has been binge drinking for the last 5 days and probably has had very little to eat. The patient's medical history is significant for alcohol-related seizures 1 year ago. He had been sober until 2 weeks ago, when he started drinking again. The patient's past medical history is otherwise unremarkable. On examination, he responds to voice but does not follow commands. Fingerstick glucose is 35 mg/dL and urine is strongly positive for ketones. Suppression of which of the following is the primary cause of this patient's hypoglycemia?

○ A. Gluconeogenesis
○ B. Glycogenolysis
○ C. Insulin clearance
○ D. Insulin sensitivity
○ E. Lipolysis

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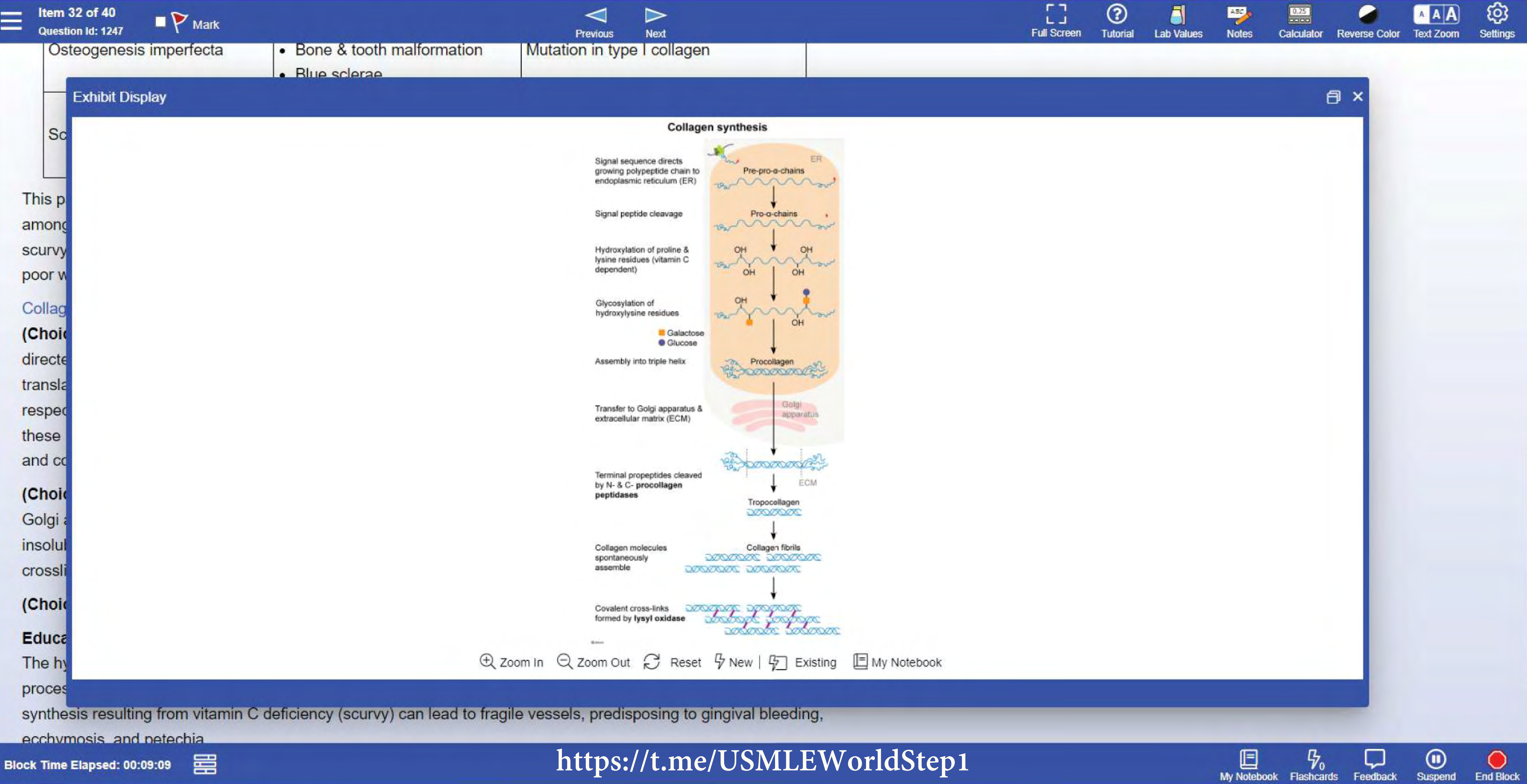
Item 32 of 40
Question Id: 1247
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
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My Notebook
Block Time Elapsed: 00:09:09
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Osteogenesis imperfecta	- Bone & tooth malformation - Blue sclerae	Mutation in type I collagen
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Collagen synthesis

Signal sequence directs growing polypeptide chain to endoplasmic reticulum (ER)
ER
Pre-pro-α-chains
Signal peptide cleavage
Pro-α-chains
Hydroxylation of proline & lysine residues (vitamin C dependent)
OH
OH
OH
OH
Glycosylation of hydroxylysine residues
OH
OH
Galactose
Glucose
Assembly into triple helix
Procollagen
Transfer to Golgi apparatus & extracellular matrix (ECM)
Golgi apparatus
Terminal propeptides cleaved by N- & C- **procollagen peptidases**
ECM
Tropocollagen
Collagen molecules spontaneously assemble
Collagen fibrils
Covalent cross-links formed by **lysyl oxidase**

Osteogenesis imperfecta	• Bone & tooth malformation • Blue sclerae	Mutation in type I collagen
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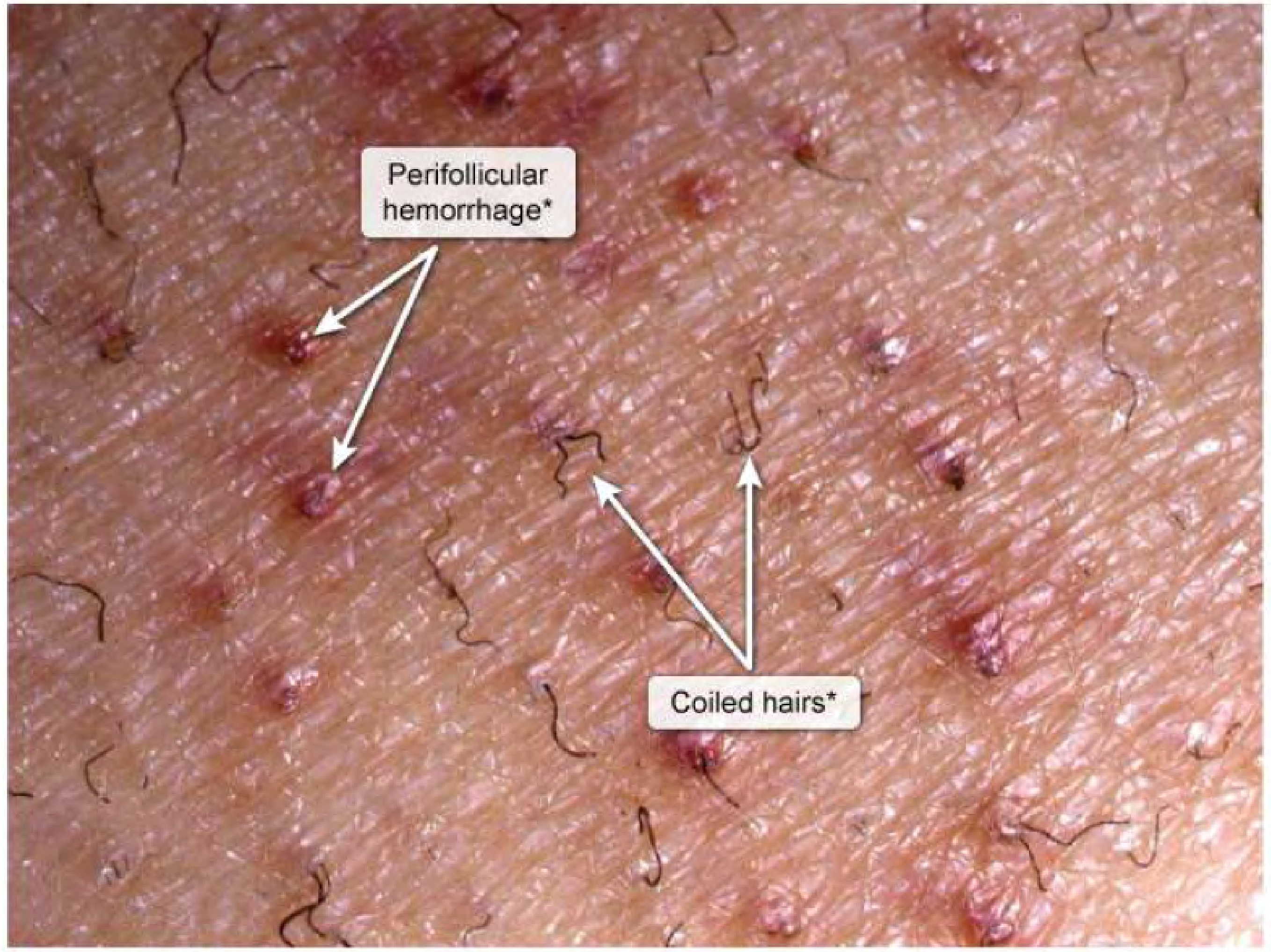
Vitamin C deficiency (scurvy)


Perifollicular hemorrhage*
Coiled hairs*

*Due to impaired collagen formation.

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Reset
New | Existing
My Notebook

Osteogenesis imperfecta	- Bone & tooth malformation - Blue sclerae	Mutation in type I collagen
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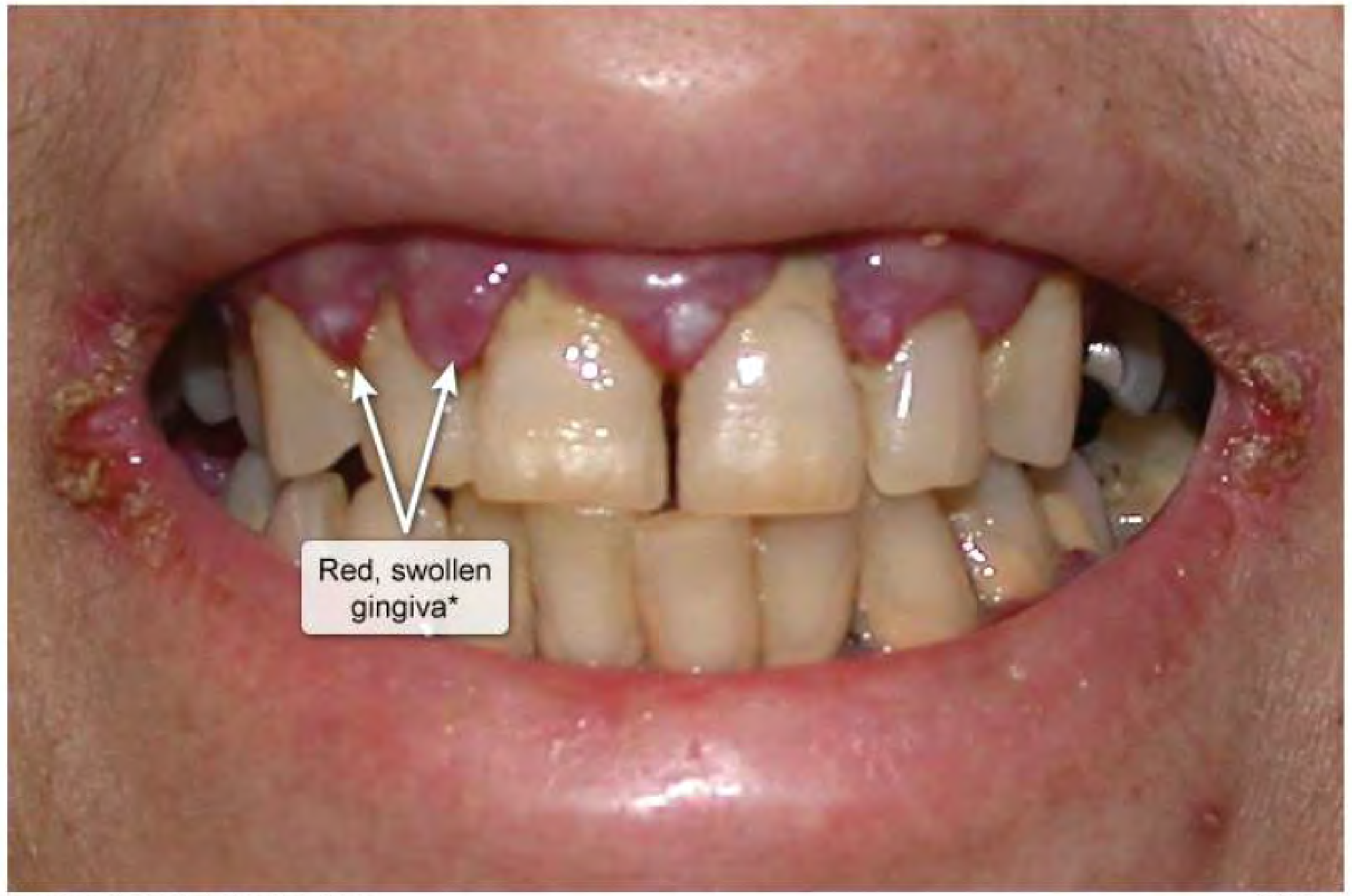
Exhibit Display

Vitamin C deficiency (scurvy)



*Due to impaired collagen formation.

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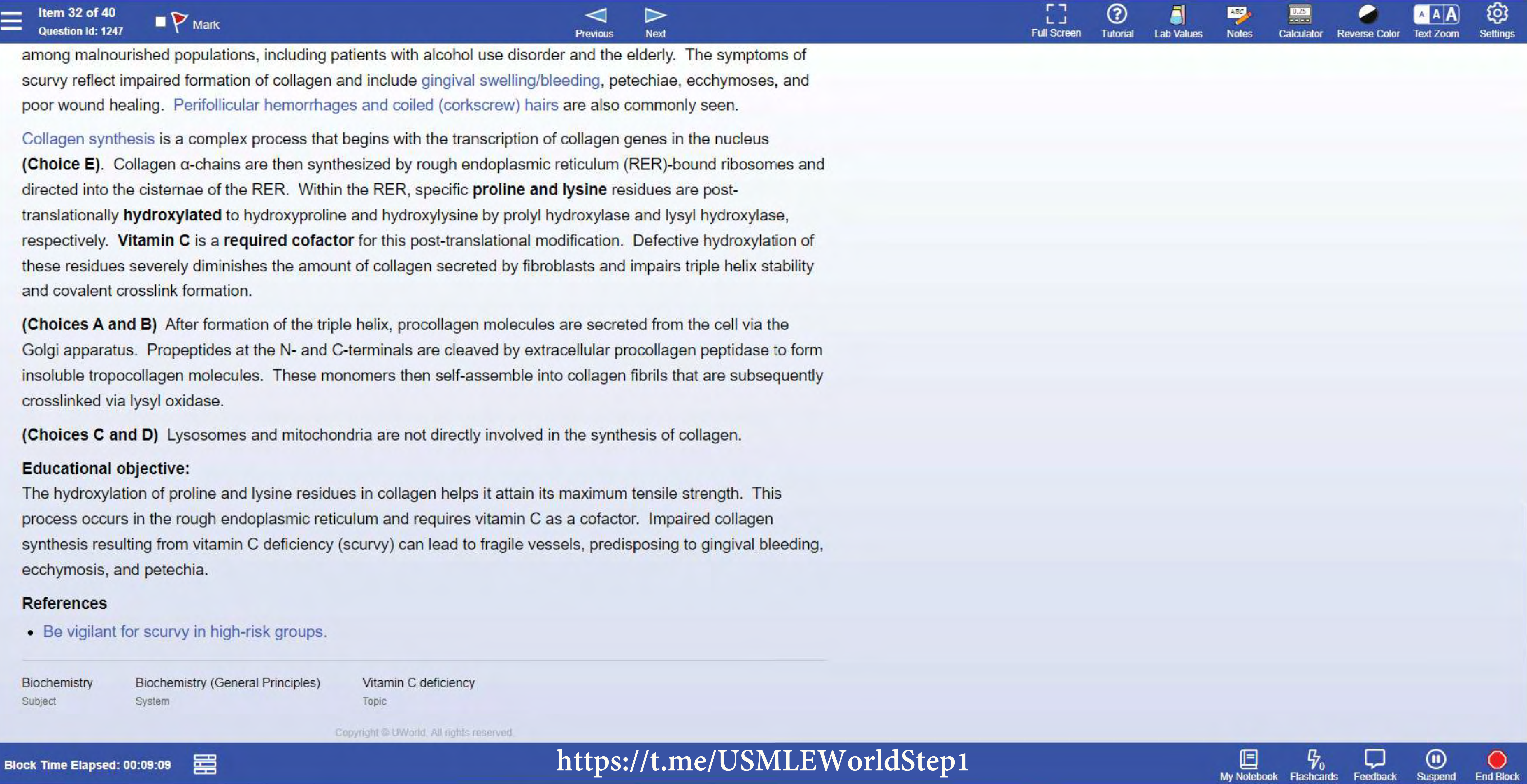

among malnourished populations, including patients with alcohol use disorder and the elderly. The symptoms of scurvy reflect impaired formation of collagen and include gingival swelling/bleeding, petechiae, ecchymoses, and poor wound healing. Perifollicular hemorrhages and coiled (corkscrew) hairs are also commonly seen.

Collagen synthesis is a complex process that begins with the transcription of collagen genes in the nucleus **(Choice E)**. Collagen α-chains are then synthesized by rough endoplasmic reticulum (RER)-bound ribosomes and directed into the cisternae of the RER. Within the RER, specific **proline and lysine** residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl hydroxylase, respectively. **Vitamin C** is a **required cofactor** for this post-translational modification. Defective hydroxylation of these residues severely diminishes the amount of collagen secreted by fibroblasts and impairs triple helix stability and covalent crosslink formation.

(Choices A and B) After formation of the triple helix, procollagen molecules are secreted from the cell via the Golgi apparatus. Propeptides at the N- and C-terminals are cleaved by extracellular procollagen peptidase to form insoluble tropocollagen molecules. These monomers then self-assemble into collagen fibrils that are subsequently crosslinked via lysyl oxidase.

(Choices C and D) Lysosomes and mitochondria are not directly involved in the synthesis of collagen.

Educational objective:
The hydroxylation of proline and lysine residues in collagen helps it attain its maximum tensile strength. This process occurs in the rough endoplasmic reticulum and requires vitamin C as a cofactor. Impaired collagen synthesis resulting from vitamin C deficiency (scurvy) can lead to fragile vessels, predisposing to gingival bleeding, ecchymosis, and petechia.

References

- Be vigilant for scurvy in high-risk groups.

Biochemistry	Biochemistry (General Principles)	Vitamin C deficiency
Subject	System	Topic

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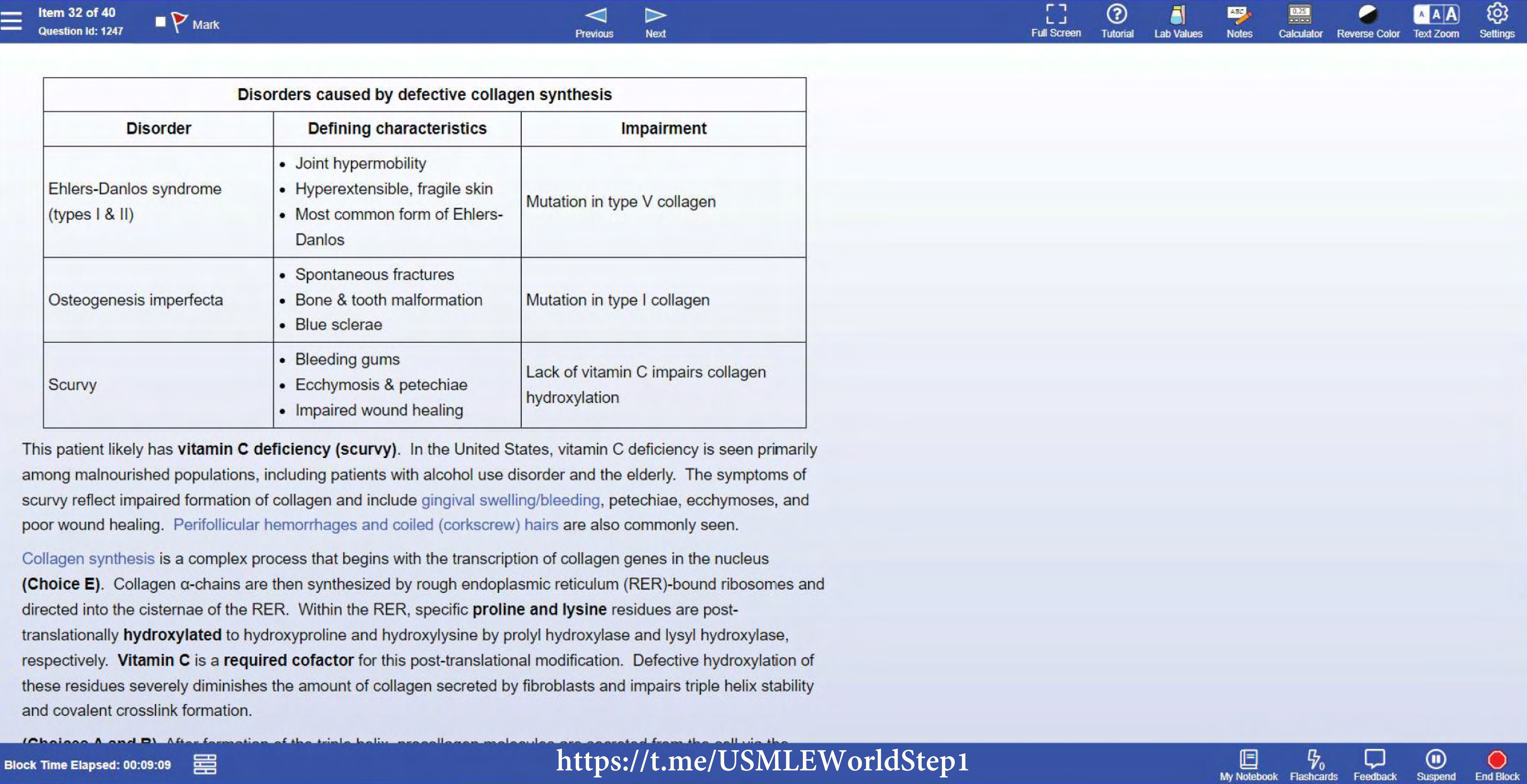
Item 32 of 40
Question Id: 1247
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Disorders caused by defective collagen synthesis		
Disorder	**Defining characteristics**	**Impairment**
Ehlers-Danlos syndrome (types I & II)	• Joint hypermobility • Hyperextensible, fragile skin • Most common form of Ehlers-Danlos	Mutation in type V collagen
Osteogenesis imperfecta	• Spontaneous fractures • Bone & tooth malformation • Blue sclerae	Mutation in type I collagen
Scurvy	• Bleeding gums • Ecchymosis & petechiae • Impaired wound healing	Lack of vitamin C impairs collagen hydroxylation

This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished populations, including patients with alcohol use disorder and the elderly. The symptoms of scurvy reflect impaired formation of collagen and include gingival swelling/bleeding, petechiae, ecchymoses, and poor wound healing. Perifollicular hemorrhages and coiled (corkscrew) hairs are also commonly seen.

Collagen synthesis is a complex process that begins with the transcription of collagen genes in the nucleus **(Choice E)**. Collagen α-chains are then synthesized by rough endoplasmic reticulum (RER)-bound ribosomes and directed into the cisternae of the RER. Within the RER, specific **proline and lysine** residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl hydroxylase, respectively. **Vitamin C** is a **required cofactor** for this post-translational modification. Defective hydroxylation of these residues severely diminishes the amount of collagen secreted by fibroblasts and impairs triple helix stability and covalent crosslink formation.

(Choices A and B). After formation of the triple helix, procollagen molecules are secreted from the cell via the

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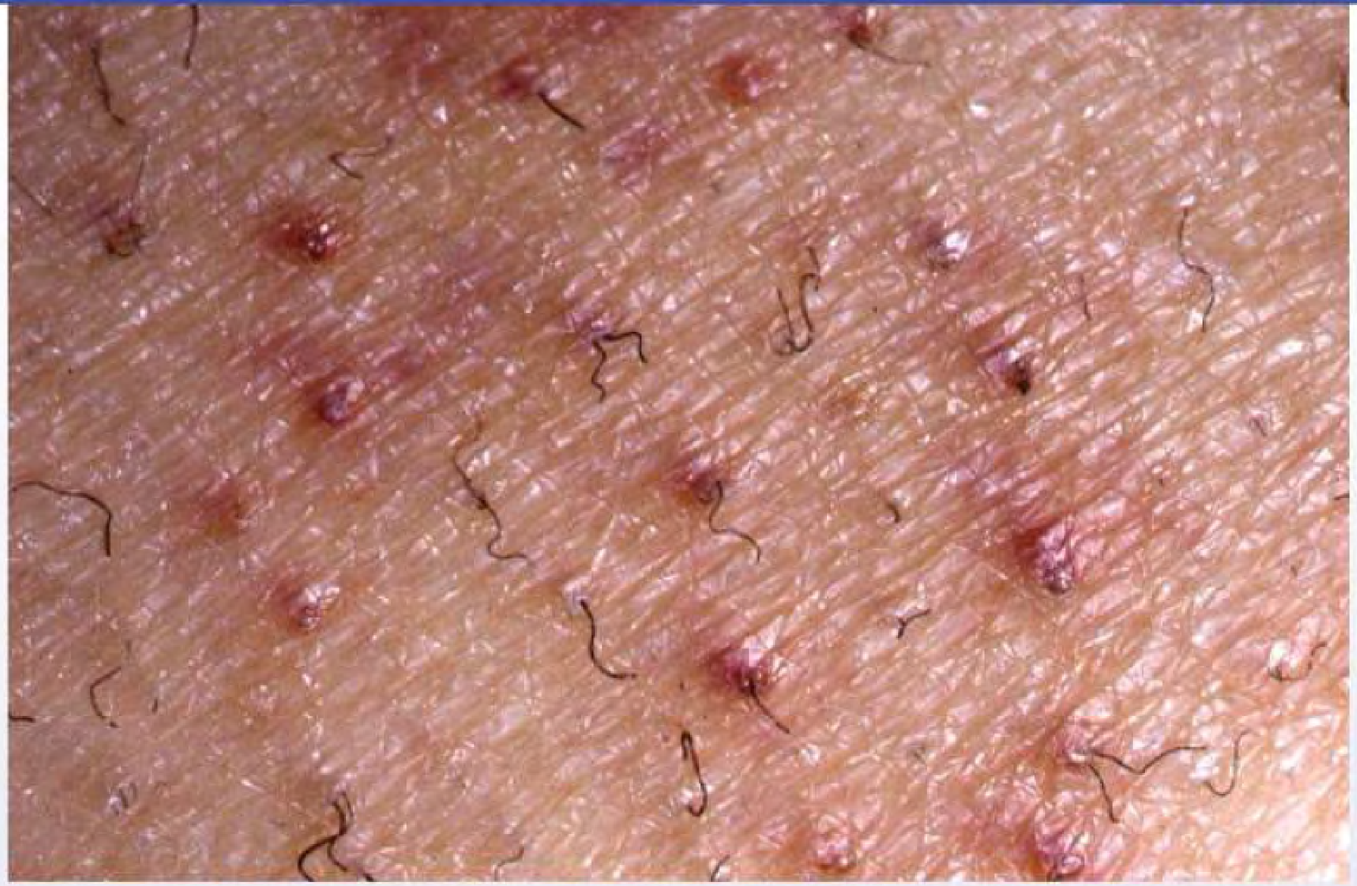

Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

- ○ A. Extracellular space (15%)
- ○ B. Golgi apparatus (14%)
- ✗ ● C. Lysosomes (4%)
- ○ D. Mitochondria (10%)
- ○ E. Nucleus (3%)
- ✓ ○ F. Rough endoplasmic reticulum (50%)

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Correct answer
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50%
Answered correctly

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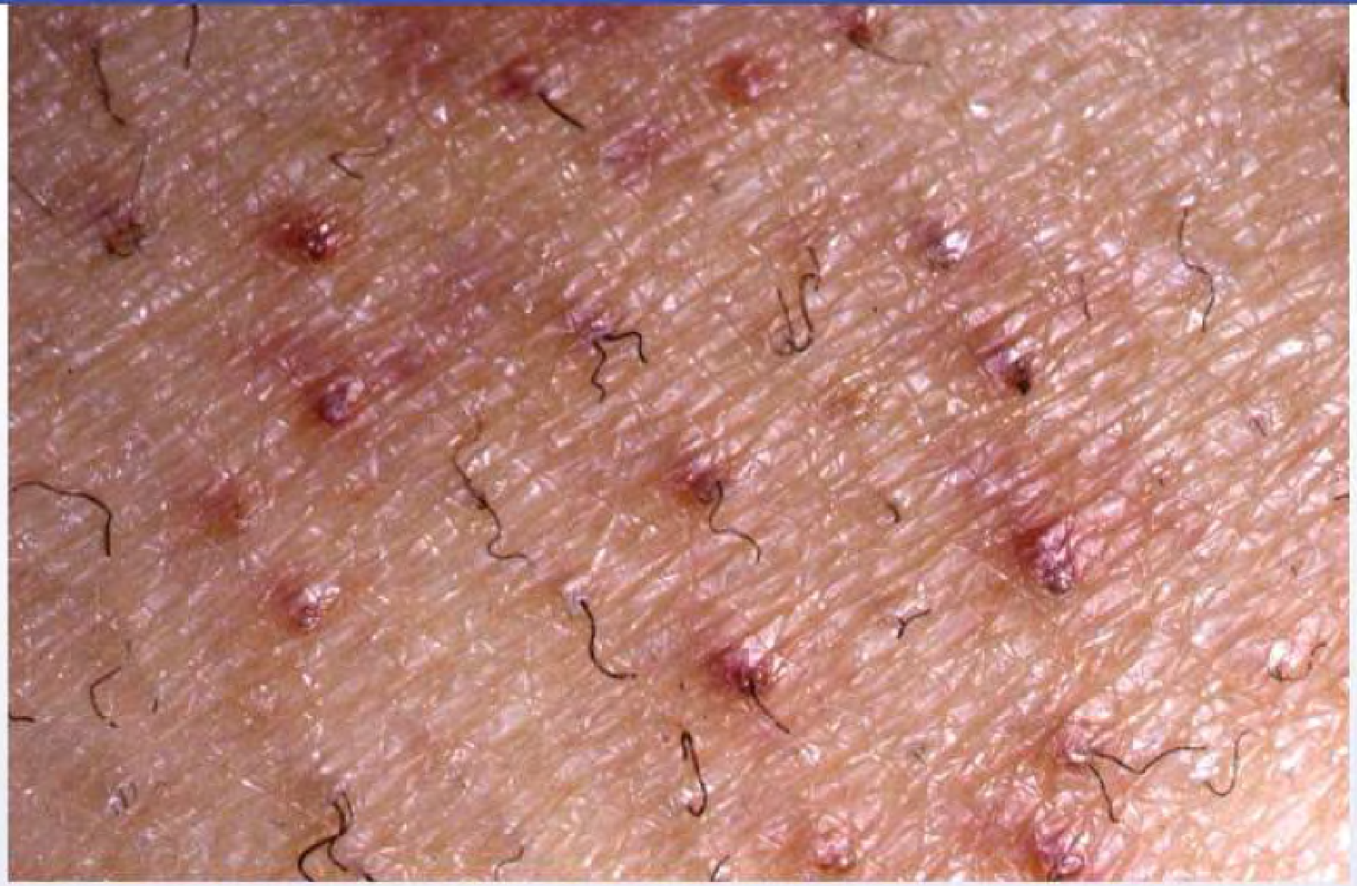
2023
Version

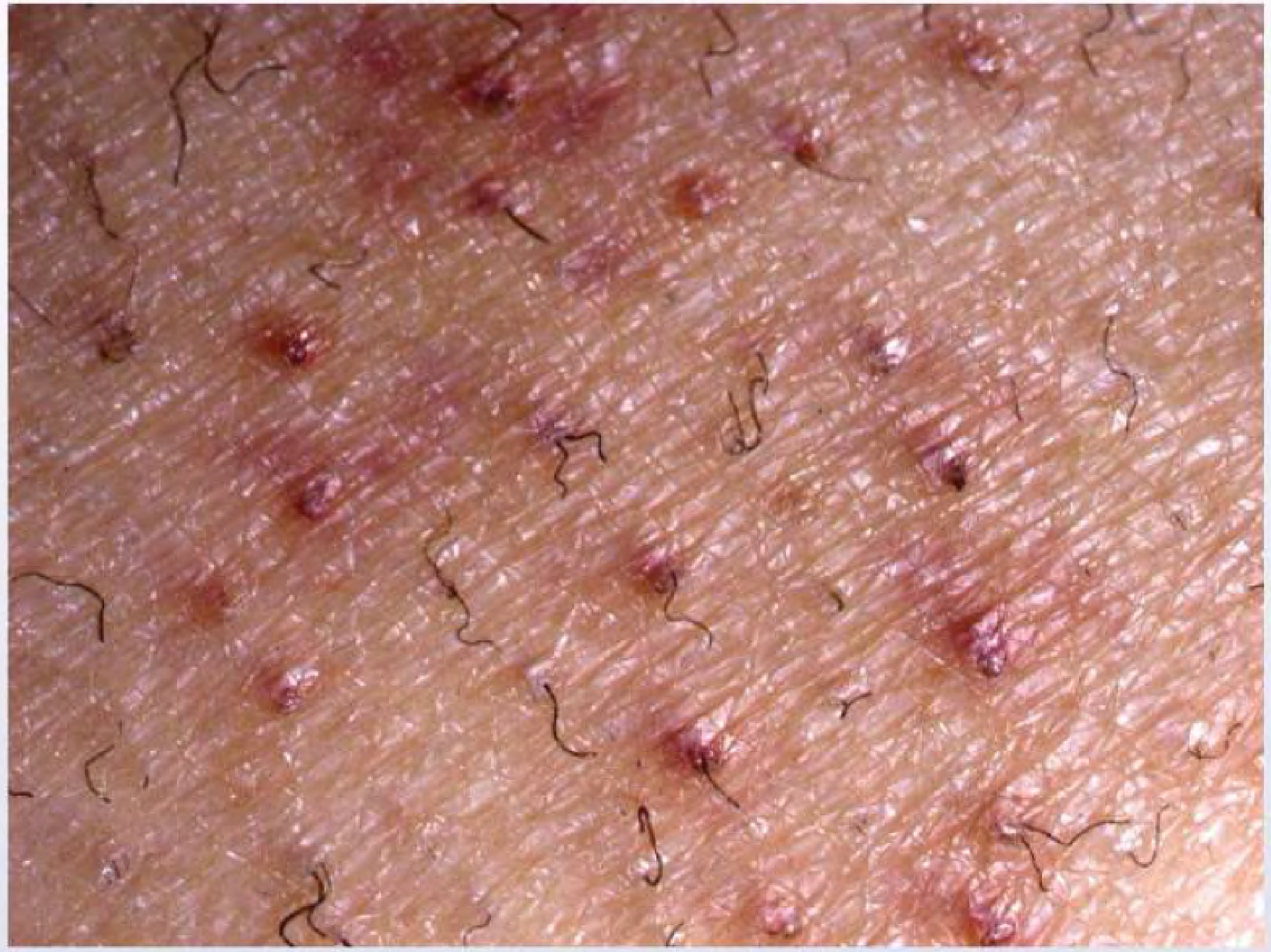


Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

- ○ A. Extracellular space
- ○ B. Golgi apparatus
- ○ C. Lysosomes
- ○ D. Mitochondria
- ○ E. Nucleus
- ○ F. Rough endoplasmic reticulum

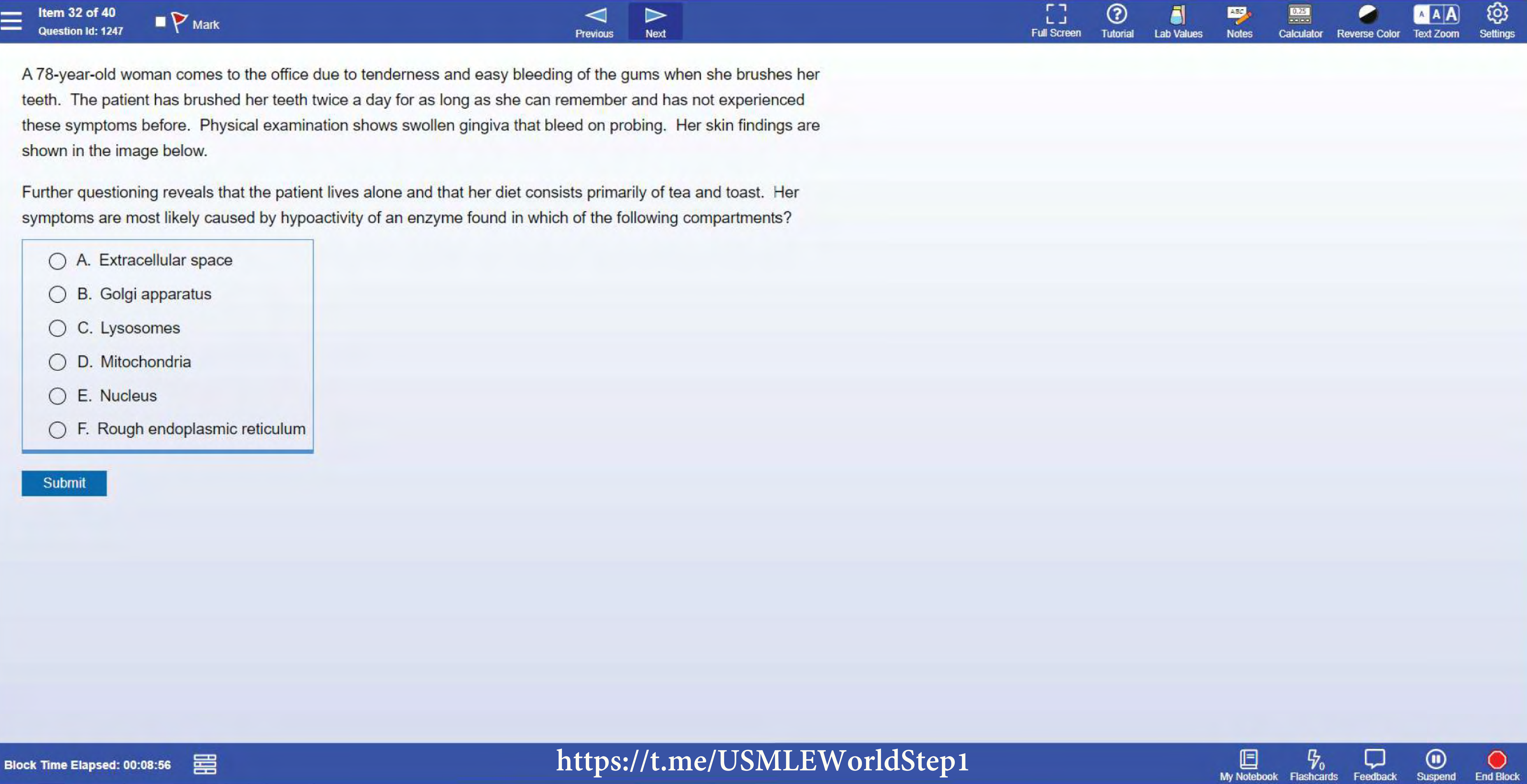
Submit

A 78-year-old woman comes to the office due to tenderness and easy bleeding of the gums when she brushes her teeth. The patient has brushed her teeth twice a day for as long as she can remember and has not experienced these symptoms before. Physical examination shows swollen gingiva that bleed on probing. Her skin findings are shown in the image below.



Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

○ A. Extracellular space
○ B. Golgi apparatus
○ C. Lysosomes


Item 32 of 40
Question Id: 1247
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 78-year-old woman comes to the office due to tenderness and easy bleeding of the gums when she brushes her teeth. The patient has brushed her teeth twice a day for as long as she can remember and has not experienced these symptoms before. Physical examination shows swollen gingiva that bleed on probing. Her skin findings are shown in the image below.

Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

○ A. Extracellular space
○ B. Golgi apparatus
○ C. Lysosomes
○ D. Mitochondria
○ E. Nucleus
○ F. Rough endoplasmic reticulum

Submit
Block Time Elapsed: 00:08:56
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 31 of 40
Question Id: 11930
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:08:56
My Notebook
Flashcards
Feedback
Suspend
End Block

space. This leads to lack of degradation of lysosomal cellular debris, which accumulates within the lysosome, forming the characteristic inclusion bodies. Patients with this disorder typically have failure to thrive, respiratory tract infections, and cognitive deficits in the first year of life, along with characteristic physical features (eg, coarse facies, corneal clouding, hepatosplenomegaly).

(Choice A) The endoplasmic reticulum (ER) is the site of protein synthesis prior to transport to the Golgi apparatus for protein modification and vesicular trafficking. Retrograde transport from the Golgi apparatus to the ER occurs via specialized protein-coated vesicles (eg, COPI).

(Choice B) Following translation in the ER, secretory proteins traverse the Golgi apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion. Lysosomal proteins are inappropriately transferred to the extracellular space in patients with I-cell disease.

(Choice D) Most mitochondrial proteins are synthesized in the cytosol and contain specific mitochondrial targeting sequences. Translocases detect these sequences and shuttle the proteins into and between the different mitochondrial compartments.

(Choice E) Peripheral membrane proteins may be modified through a process in which a hydrophobic lipid anchor is covalently attached to the protein. This process facilitates protein interaction with the plasma membrane.

Educational objective:

Inclusion cell disease is a lysosomal storage disorder in which a defect in protein targeting prevents the phosphorylation of mannose residues required to tag acid hydrolases for transport to lysosomes. Without these lysosomal proteins, cellular debris cannot be degraded and therefore accumulates within lysosomes, forming inclusion bodies characteristic of the disease.

References

- Mucolipidoses overview: past, present, and future.

Biochemistry	Biochemistry (General Principles)	Lysosomal storage disorder
Subject	System	Topic

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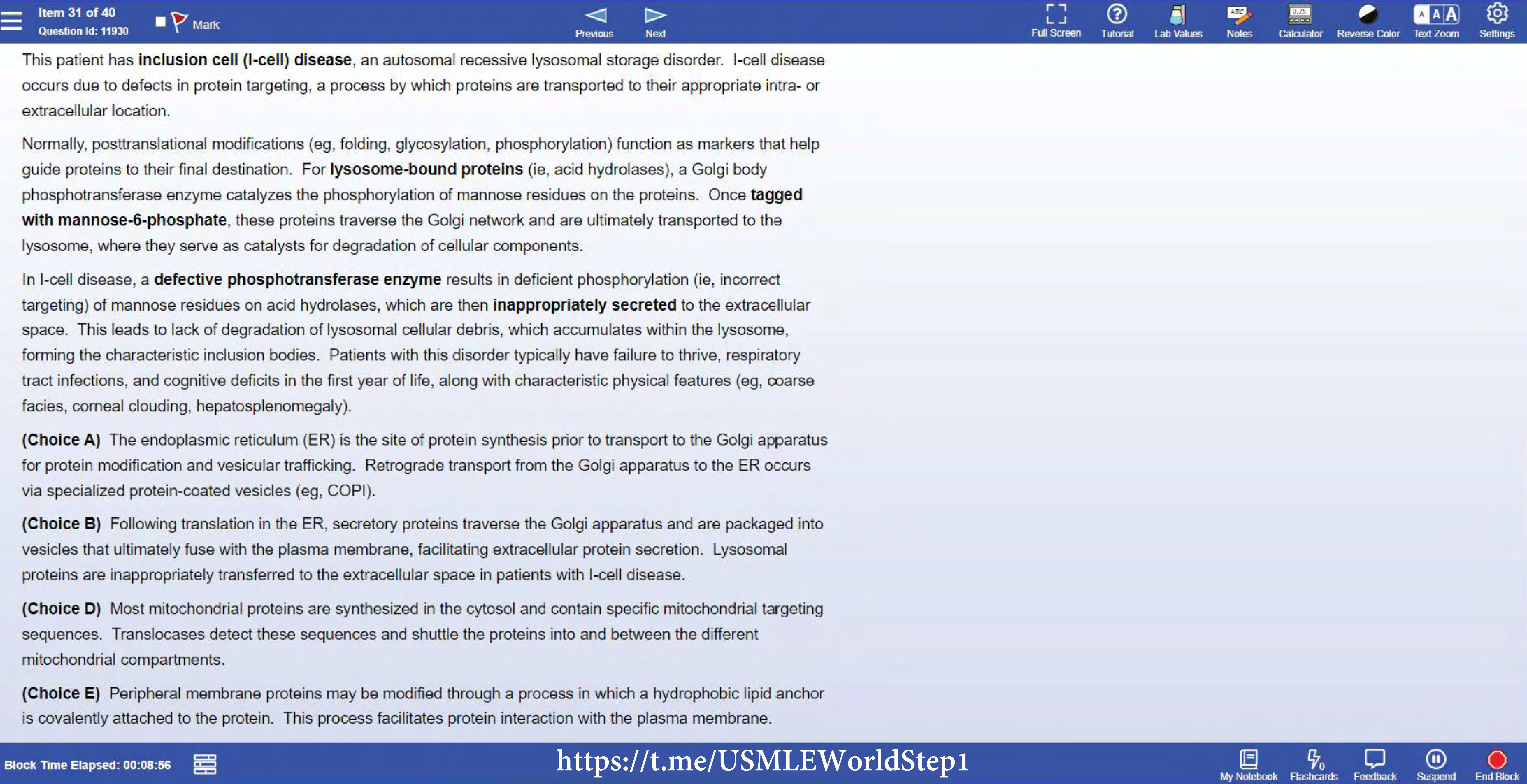

This patient has **inclusion cell (I-cell) disease**, an autosomal recessive lysosomal storage disorder. I-cell disease occurs due to defects in protein targeting, a process by which proteins are transported to their appropriate intra- or extracellular location.

Normally, posttranslational modifications (eg, folding, glycosylation, phosphorylation) function as markers that help guide proteins to their final destination. For **lysosome-bound proteins** (ie, acid hydrolases), a Golgi body phosphotransferase enzyme catalyzes the phosphorylation of mannose residues on the proteins. Once **tagged with mannose-6-phosphate**, these proteins traverse the Golgi network and are ultimately transported to the lysosome, where they serve as catalysts for degradation of cellular components.

In I-cell disease, a **defective phosphotransferase enzyme** results in deficient phosphorylation (ie, incorrect targeting) of mannose residues on acid hydrolases, which are then **inappropriately secreted** to the extracellular space. This leads to lack of degradation of lysosomal cellular debris, which accumulates within the lysosome, forming the characteristic inclusion bodies. Patients with this disorder typically have failure to thrive, respiratory tract infections, and cognitive deficits in the first year of life, along with characteristic physical features (eg, coarse facies, corneal clouding, hepatosplenomegaly).

(Choice A) The endoplasmic reticulum (ER) is the site of protein synthesis prior to transport to the Golgi apparatus for protein modification and vesicular trafficking. Retrograde transport from the Golgi apparatus to the ER occurs via specialized protein-coated vesicles (eg, COPI).

(Choice B) Following translation in the ER, secretory proteins traverse the Golgi apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion. Lysosomal proteins are inappropriately transferred to the extracellular space in patients with I-cell disease.

(Choice D) Most mitochondrial proteins are synthesized in the cytosol and contain specific mitochondrial targeting sequences. Translocases detect these sequences and shuttle the proteins into and between the different mitochondrial compartments.

(Choice E) Peripheral membrane proteins may be modified through a process in which a hydrophobic lipid anchor is covalently attached to the protein. This process facilitates protein interaction with the plasma membrane.

Item 31 of 40
Question Id: 11930

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Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Explanation

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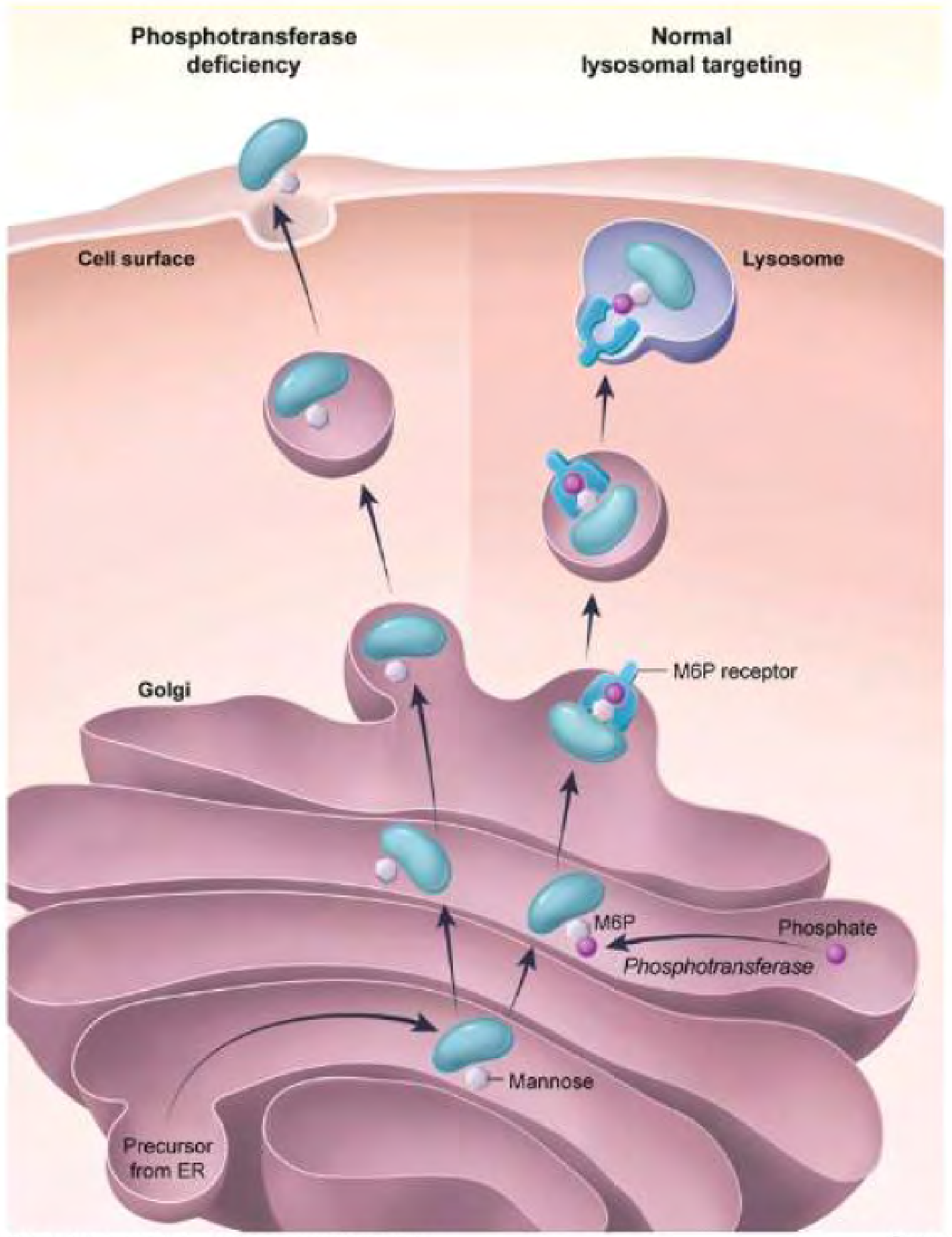
Phosphotransferase deficiency
Normal lysosomal targeting
Cell surface
Lysosome
Golgi
M6P receptor
M6P
Phosphate
Phosphotransferase
Mannose
Precursor from ER

ER = endoplasmic reticulum; **M6P** = mannose-6-phosphate.

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Block Time Elapsed: 00:08:56

My Notebook Flashcards Feedback Suspend End Block

A 2-year-old boy is being evaluated at the office for failure to thrive and developmental delay. Medical history is significant for recurrent ear infections since 6 months of age. Physical examination shows corneal clouding, hepatosplenomegaly, and restricted joint mobility. Further evaluation shows deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. In unaffected patients, these proteins are normally transported to which of the following cellular locations?

- ✗ ● A. Endoplasmic reticulum (5%)
- ○ B. Extracellular space (6%)
- ✓ ○ C. Lysosome (73%)
- ○ D. Mitochondria (1%)
- ○ E. Plasma membrane (12%)

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Correct answer
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73%
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Version

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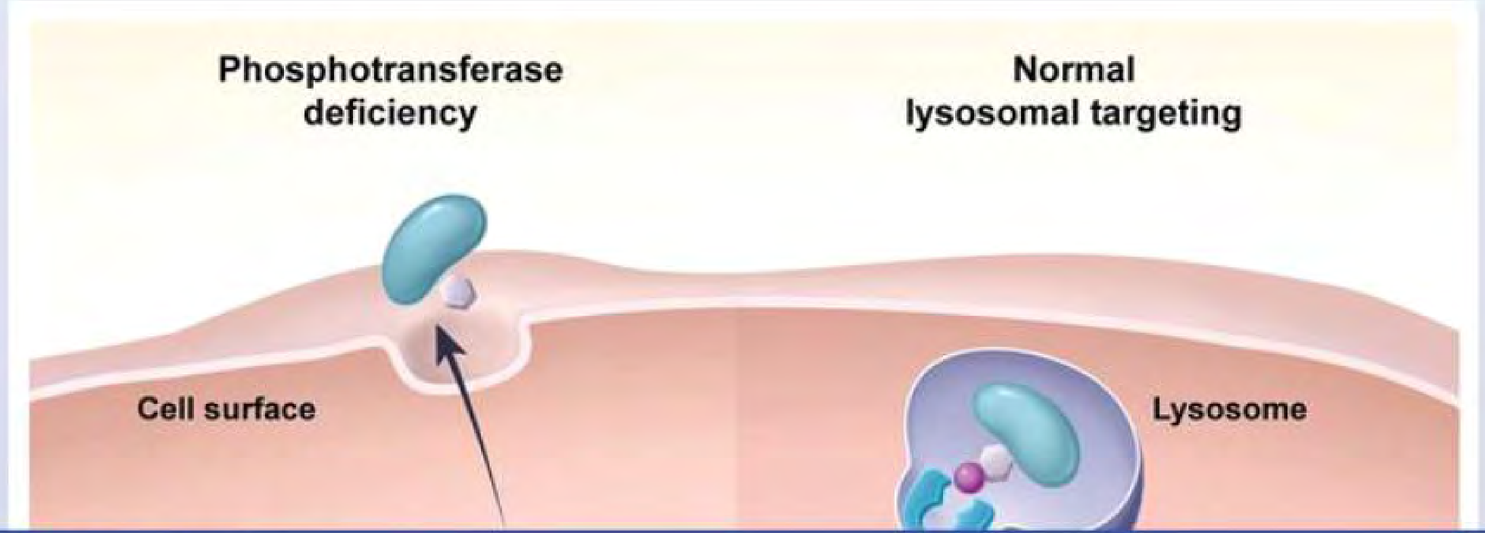

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 31 of 40
Question Id: 11930

A 2-year-old boy is being evaluated at the office for failure to thrive and developmental delay. Medical history is significant for recurrent ear infections since 6 months of age. Physical examination shows corneal clouding, hepatosplenomegaly, and restricted joint mobility. Further evaluation shows deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. In unaffected patients, these proteins are normally transported to which of the following cellular locations?

○ A. Endoplasmic reticulum
○ B. Extracellular space
○ C. Lysosome
○ D. Mitochondria
○ E. Plasma membrane

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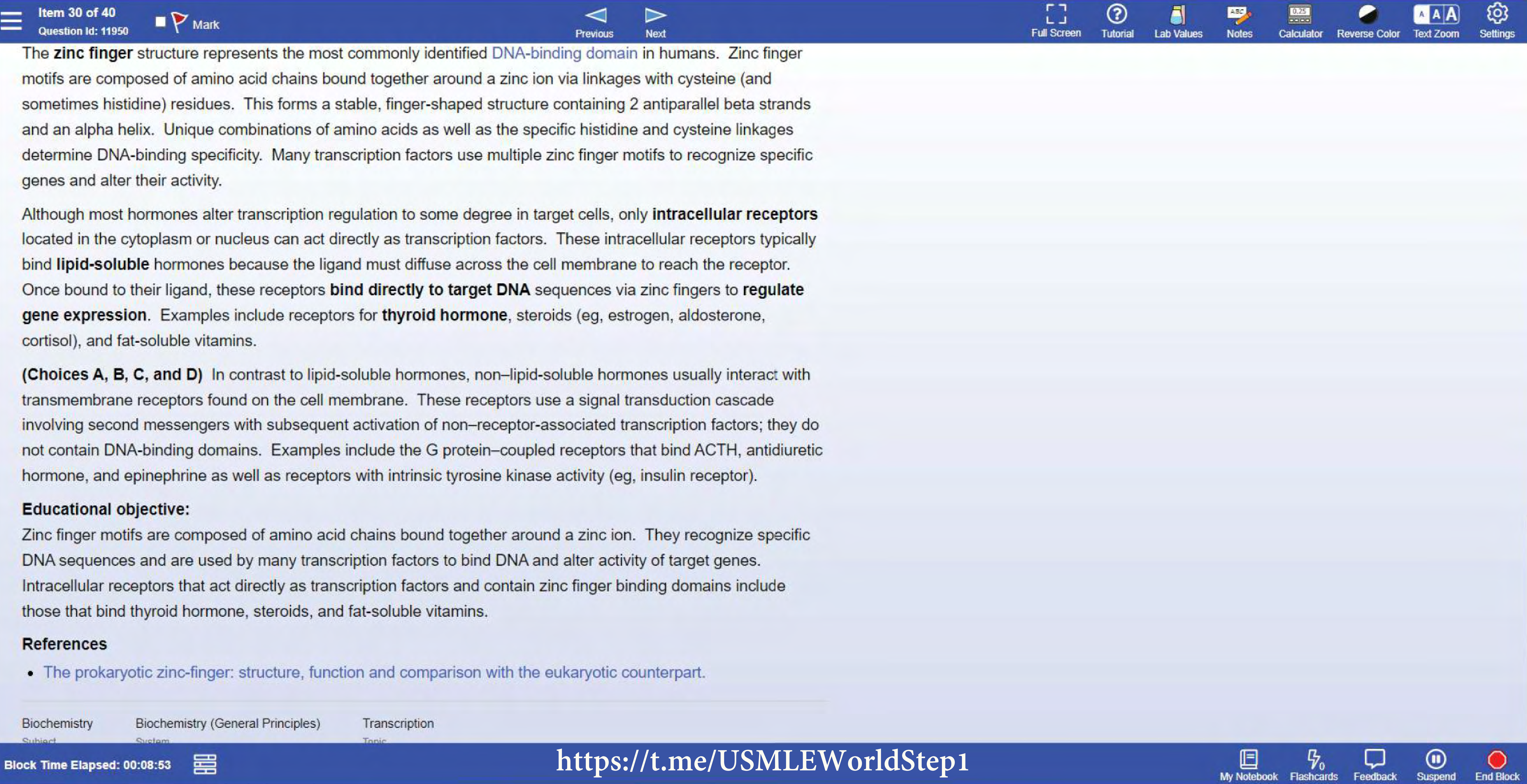

The **zinc finger** structure represents the most commonly identified DNA-binding domain in humans. Zinc finger motifs are composed of amino acid chains bound together around a zinc ion via linkages with cysteine (and sometimes histidine) residues. This forms a stable, finger-shaped structure containing 2 antiparallel beta strands and an alpha helix. Unique combinations of amino acids as well as the specific histidine and cysteine linkages determine DNA-binding specificity. Many transcription factors use multiple zinc finger motifs to recognize specific genes and alter their activity.

Although most hormones alter transcription regulation to some degree in target cells, only **intracellular receptors** located in the cytoplasm or nucleus can act directly as transcription factors. These intracellular receptors typically bind **lipid-soluble** hormones because the ligand must diffuse across the cell membrane to reach the receptor. Once bound to their ligand, these receptors **bind directly to target DNA** sequences via zinc fingers to **regulate gene expression**. Examples include receptors for **thyroid hormone**, steroids (eg, estrogen, aldosterone, cortisol), and fat-soluble vitamins.

(Choices A, B, C, and D) In contrast to lipid-soluble hormones, non–lipid-soluble hormones usually interact with transmembrane receptors found on the cell membrane. These receptors use a signal transduction cascade involving second messengers with subsequent activation of non–receptor-associated transcription factors; they do not contain DNA-binding domains. Examples include the G protein–coupled receptors that bind ACTH, antidiuretic hormone, and epinephrine as well as receptors with intrinsic tyrosine kinase activity (eg, insulin receptor).

Educational objective:

Zinc finger motifs are composed of amino acid chains bound together around a zinc ion. They recognize specific DNA sequences and are used by many transcription factors to bind DNA and alter activity of target genes. Intracellular receptors that act directly as transcription factors and contain zinc finger binding domains include those that bind thyroid hormone, steroids, and fat-soluble vitamins.

References

- The prokaryotic zinc-finger: structure, function and comparison with the eukaryotic counterpart.

Biochemistry	Biochemistry (General Principles)	Transcription
Subject	System	Topic

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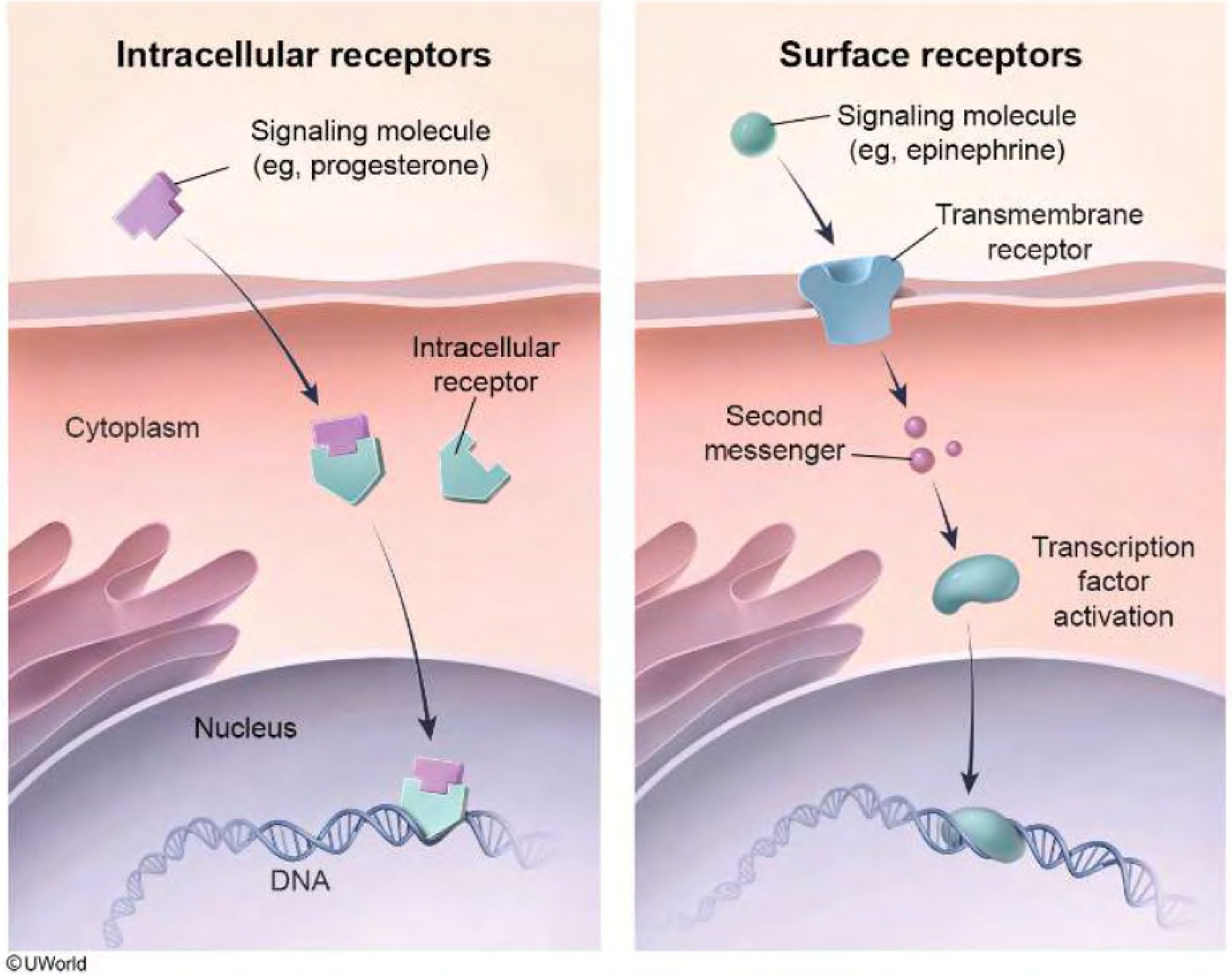
Intracellular receptors
Signaling molecule (eg, progesterone)
Intracellular receptor
Cytoplasm
Nucleus
DNA
Surface receptors
Signaling molecule (eg, epinephrine)
Transmembrane receptor
Second messenger
Transcription factor activation

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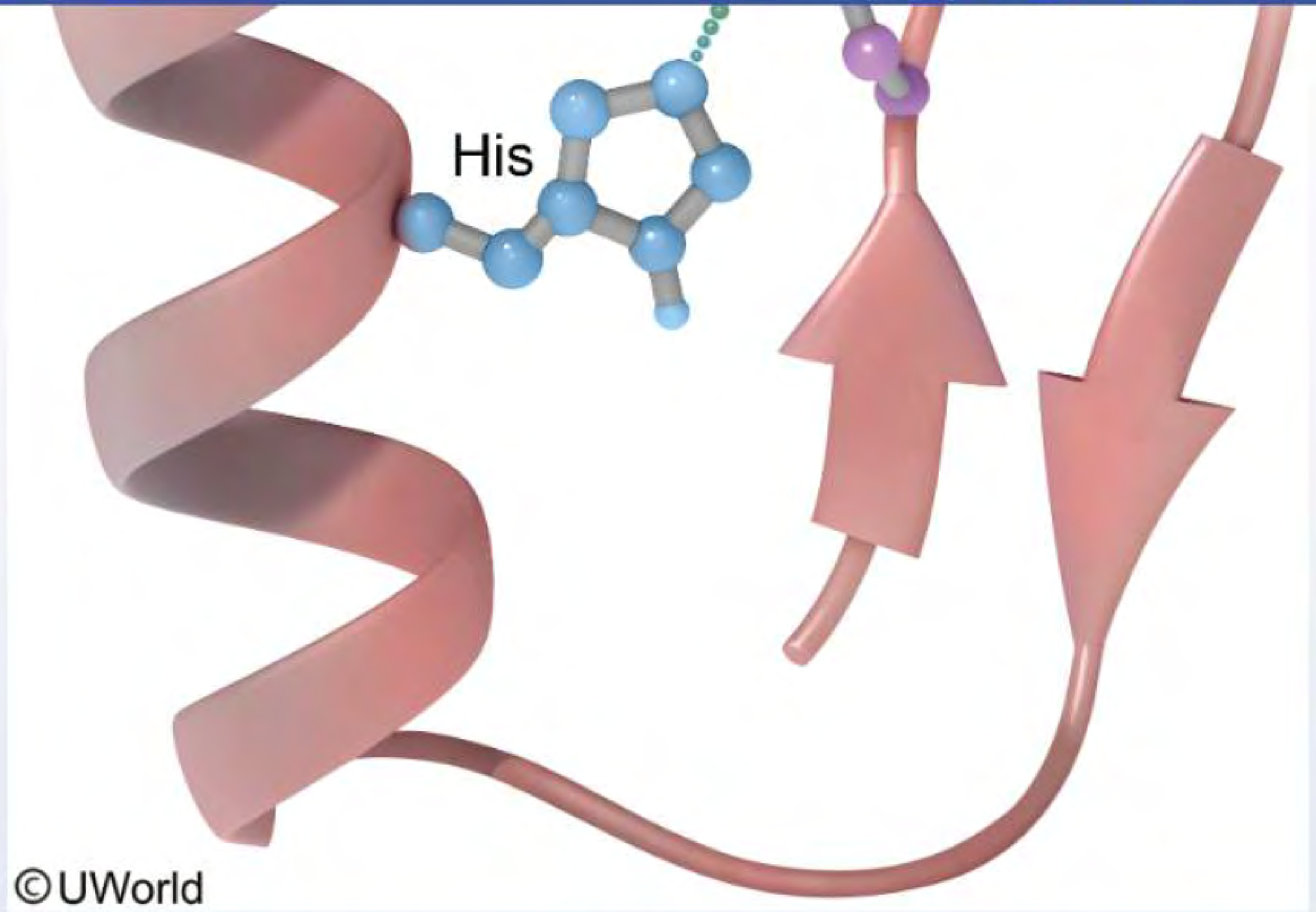
Although most hormones alter transcription regulation to some degree in target cells, only **intracellular receptors**



Which of the following hormones most likely binds to the receptor containing this structure?

- ○ A. ACTH (14%)
- ✗ ● B. Antidiuretic hormone (7%)
- ○ C. Epinephrine (11%)
- ○ D. Insulin (22%)
- ✓ ○ E. Thyroid hormone (40%)

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Correct answer
E

40%
Answered correctly

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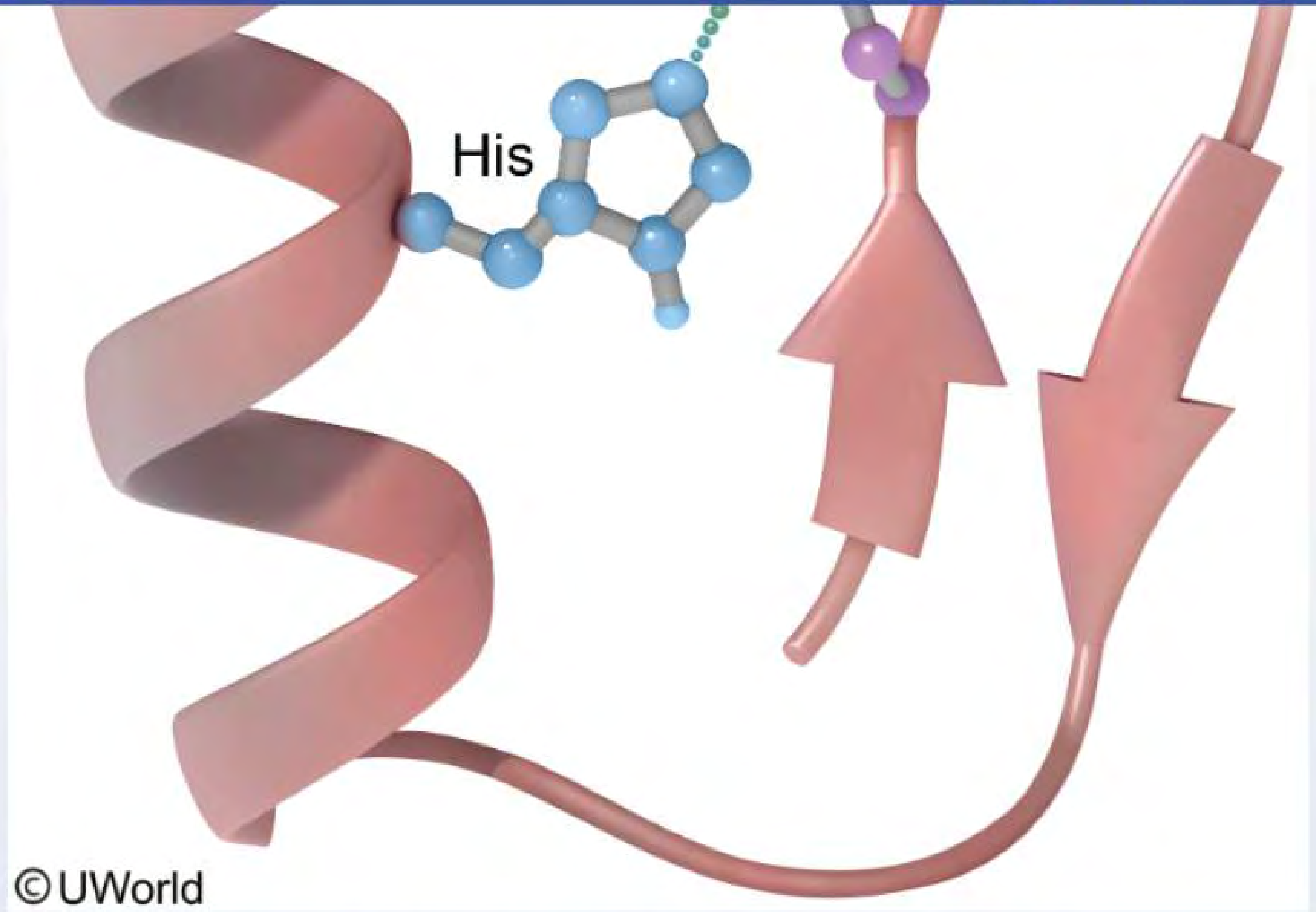

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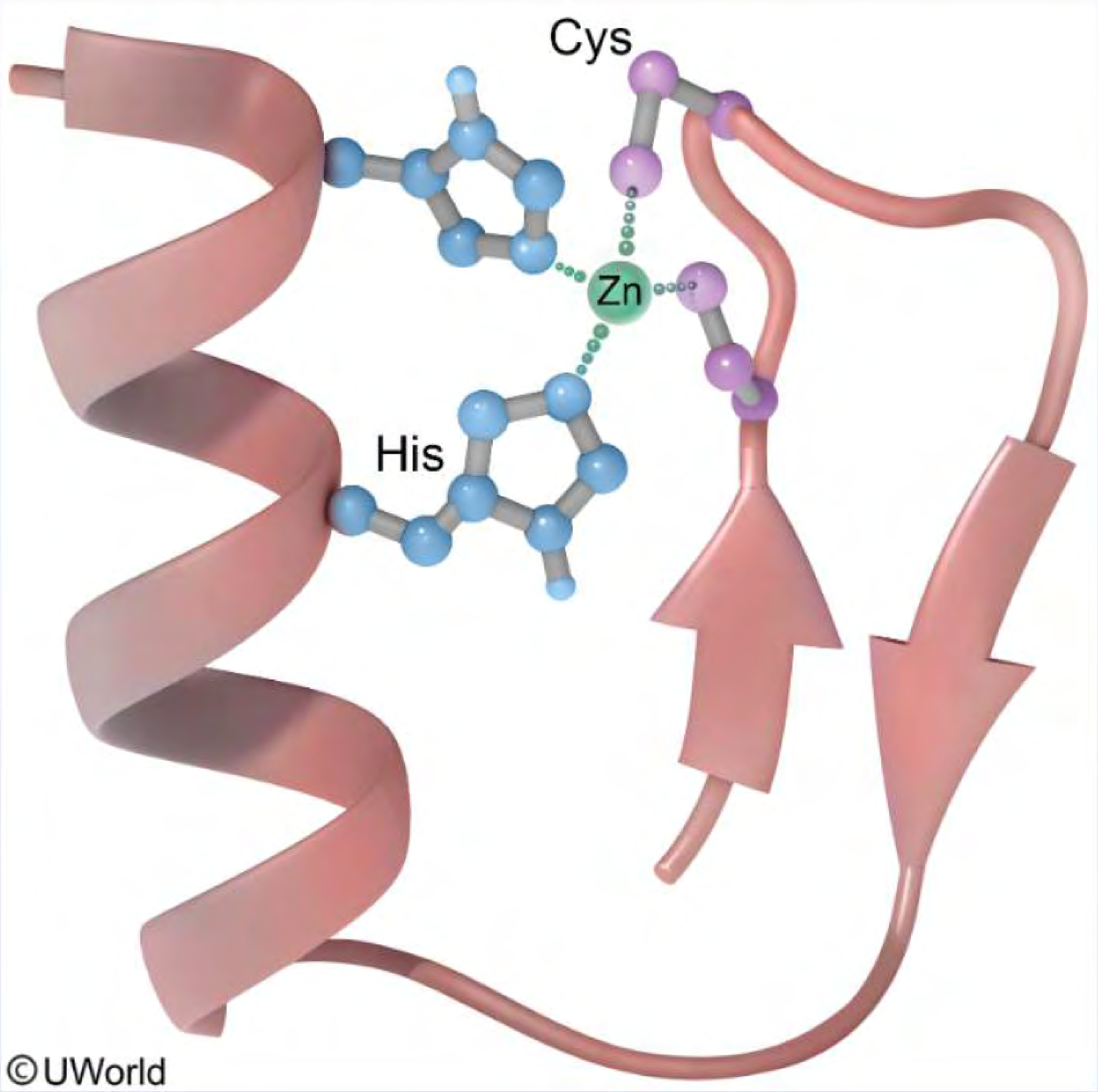
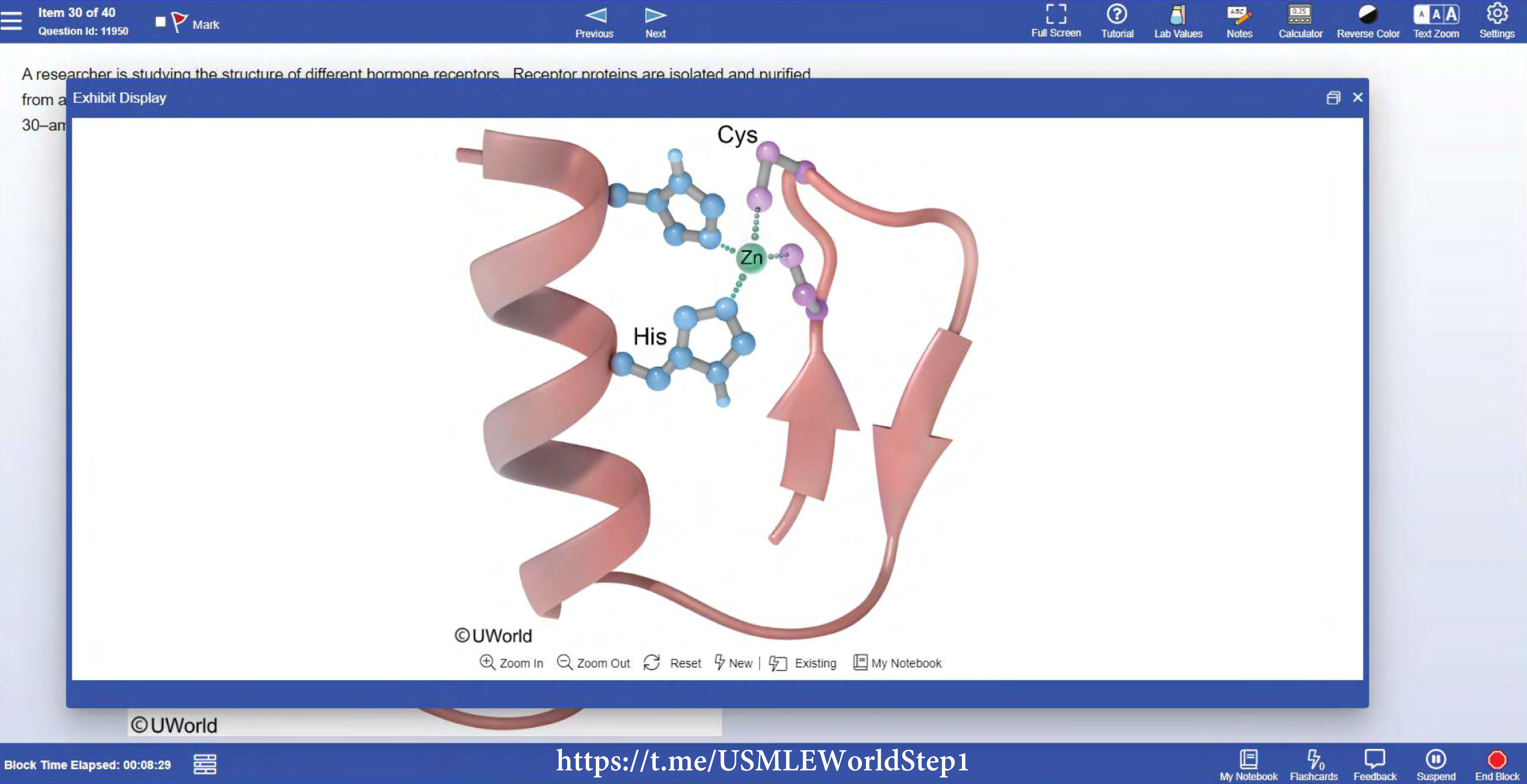
Which of the following hormones most likely binds to the receptor containing this structure?

○ A. ACTH
○ B. Antidiuretic hormone
○ C. Epinephrine
○ D. Insulin
○ E. Thyroid hormone

Submit

A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the receptor proteins contains a 30–amino acid motif coordinating a zinc ion, as shown below.





Item 30 of 40
Question Id: 11950
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified

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Flashcards
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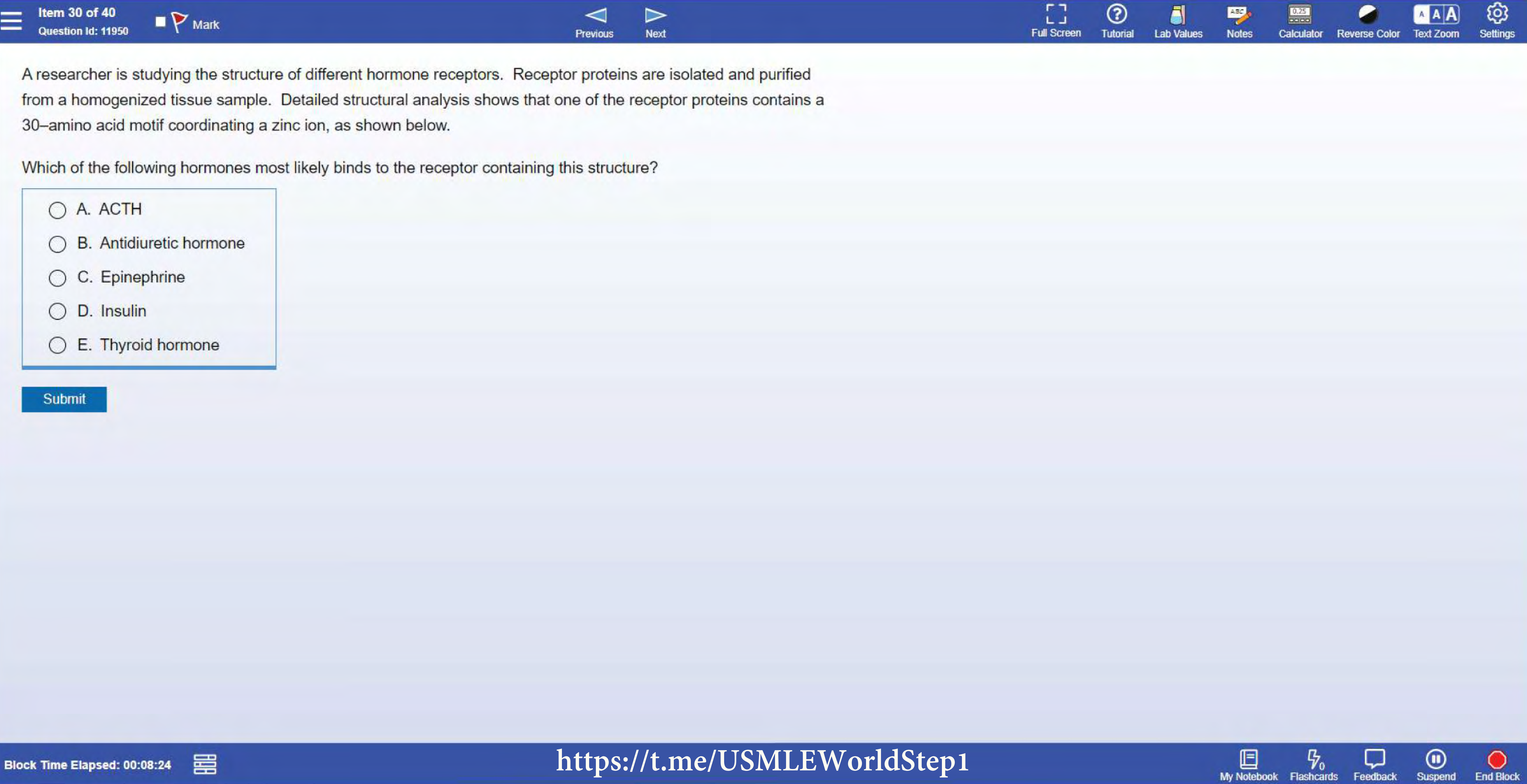
Item 30 of 40
Question Id: 11950
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
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My Notebook
Flashcards
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Suspend
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A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the receptor proteins contains a 30–amino acid motif coordinating a zinc ion, as shown below.

Which of the following hormones most likely binds to the receptor containing this structure?

- ○ A. ACTH
- ○ B. Antidiuretic hormone
- ○ C. Epinephrine
- ○ D. Insulin
- ○ E. Thyroid hormone

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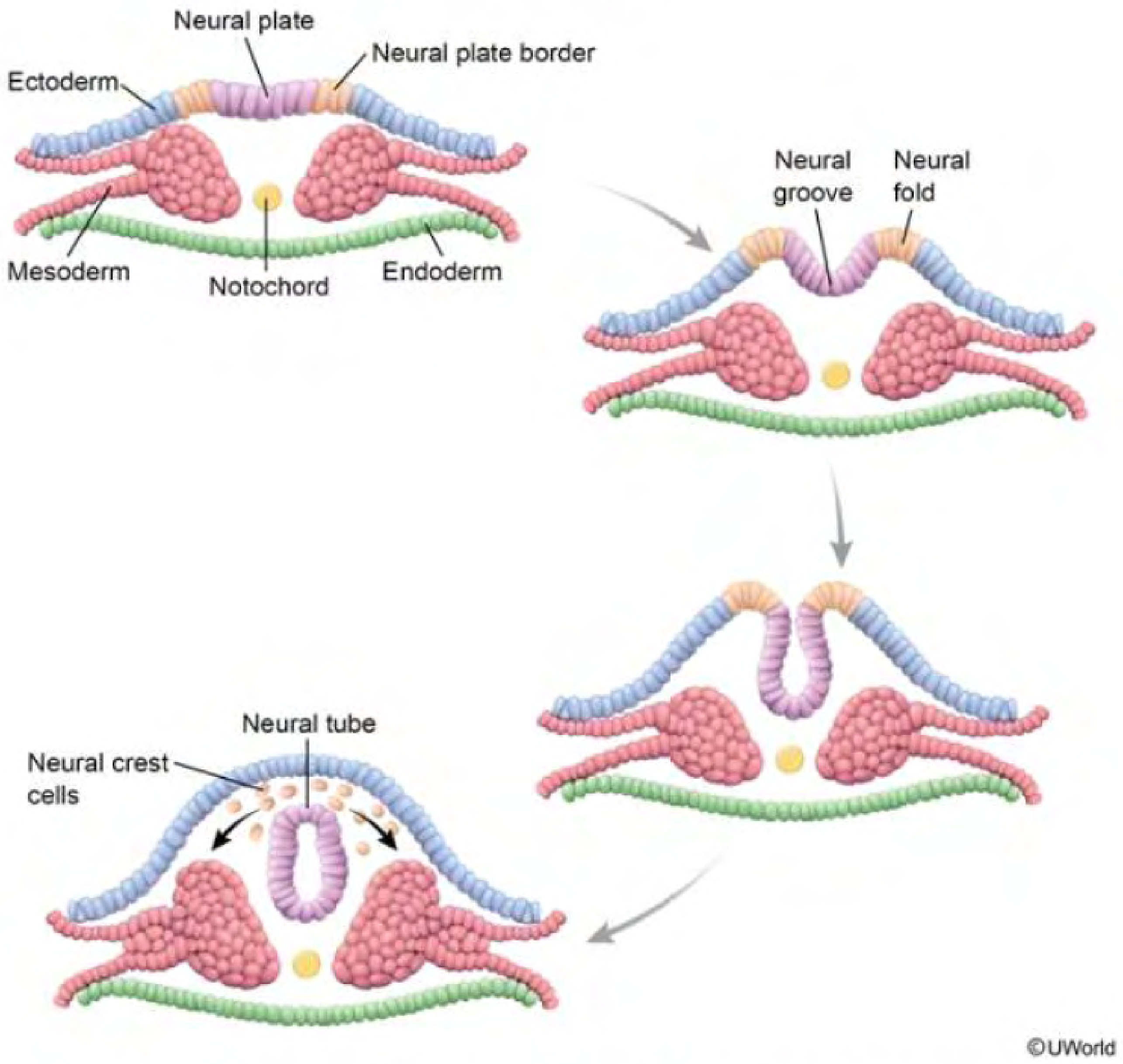
Neural plate
Neural plate border
Ectoderm
Mesoderm
Notochord
Endoderm
Neural groove
Neural fold
Neural tube
Neural crest cells

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My Notebook

(Choice B) Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral symptoms (eg, developmental delay, self-mutilating behavior). This condition is inherited in an X-linked recessive

Explanation

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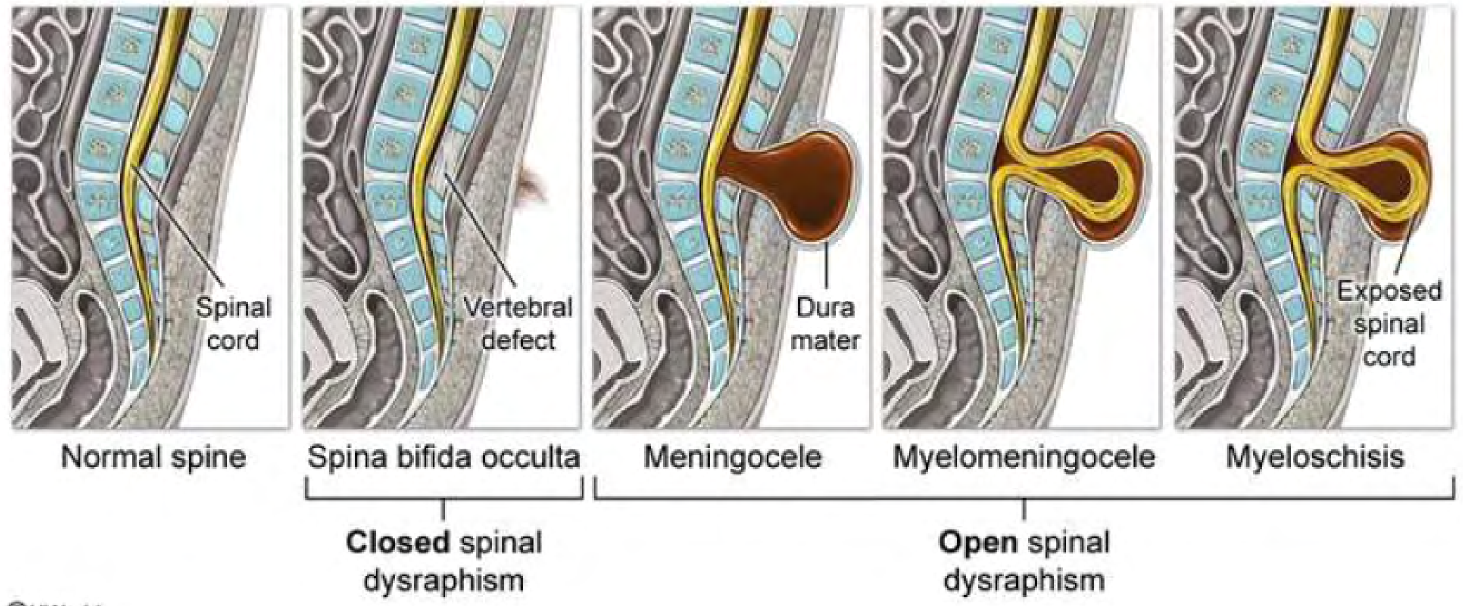
Spina bifida


Spinal cord
Vertebral defect
Dura mater
Exposed spinal cord
Normal spine
Spina bifida occulta
Meningocele
Myelomeningocele
Myeloschisis
Closed spinal dysraphism
Open spinal dysraphism

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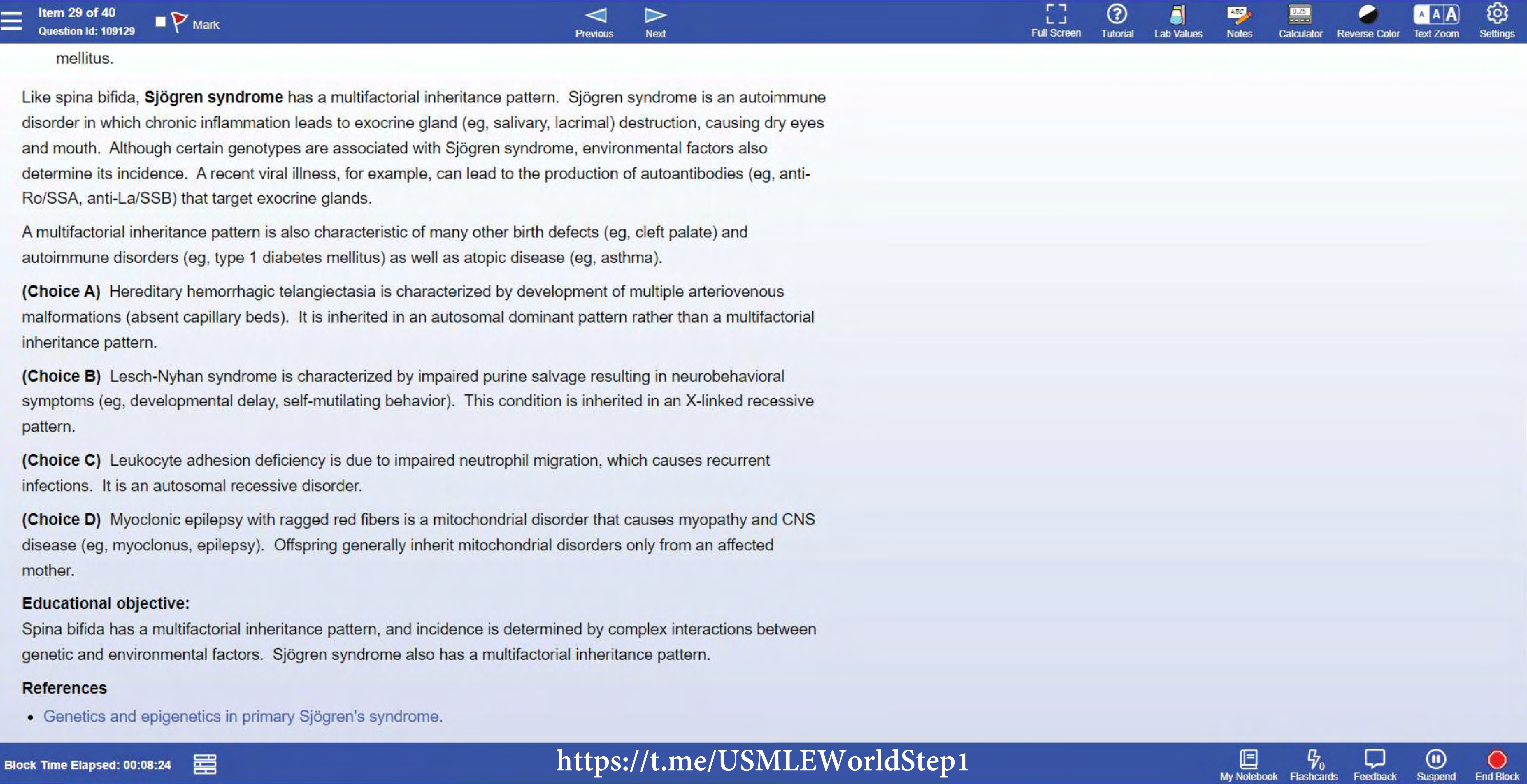
(Choice B) Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral symptoms (eg, developmental delay, self-mutilating behavior). This condition is inherited in an X-linked recessive



Item 29 of 40
Question Id: 109129
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

mellitus.

Like spina bifida, **Sjögren syndrome** has a multifactorial inheritance pattern. Sjögren syndrome is an autoimmune disorder in which chronic inflammation leads to exocrine gland (eg, salivary, lacrimal) destruction, causing dry eyes and mouth. Although certain genotypes are associated with Sjögren syndrome, environmental factors also determine its incidence. A recent viral illness, for example, can lead to the production of autoantibodies (eg, anti-Ro/SSA, anti-La/SSB) that target exocrine glands.

A multifactorial inheritance pattern is also characteristic of many other birth defects (eg, cleft palate) and autoimmune disorders (eg, type 1 diabetes mellitus) as well as atopic disease (eg, asthma).

(Choice A) Hereditary hemorrhagic telangiectasia is characterized by development of multiple arteriovenous malformations (absent capillary beds). It is inherited in an autosomal dominant pattern rather than a multifactorial inheritance pattern.

(Choice B) Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral symptoms (eg, developmental delay, self-mutilating behavior). This condition is inherited in an X-linked recessive pattern.

(Choice C) Leukocyte adhesion deficiency is due to impaired neutrophil migration, which causes recurrent infections. It is an autosomal recessive disorder.

(Choice D) Myoclonic epilepsy with ragged red fibers is a mitochondrial disorder that causes myopathy and CNS disease (eg, myoclonus, epilepsy). Offspring generally inherit mitochondrial disorders only from an affected mother.

Educational objective:

Spina bifida has a multifactorial inheritance pattern, and incidence is determined by complex interactions between genetic and environmental factors. Sjögren syndrome also has a multifactorial inheritance pattern.

References

- Genetics and epigenetics in primary Sjögren's syndrome.

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Feedback
Suspend
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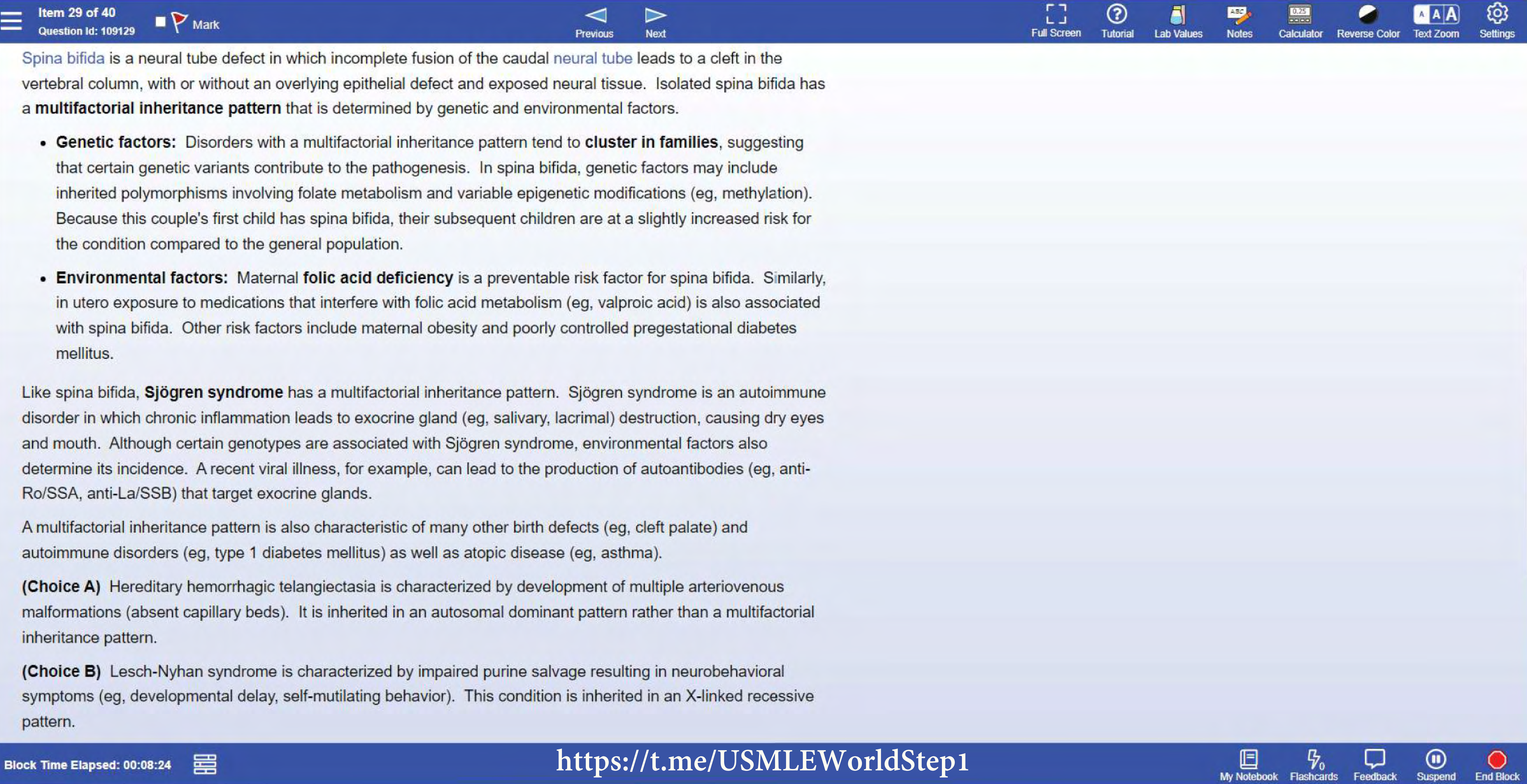


Spina bifida is a neural tube defect in which incomplete fusion of the caudal neural tube leads to a cleft in the vertebral column, with or without an overlying epithelial defect and exposed neural tissue. Isolated spina bifida has a **multifactorial inheritance pattern** that is determined by genetic and environmental factors.

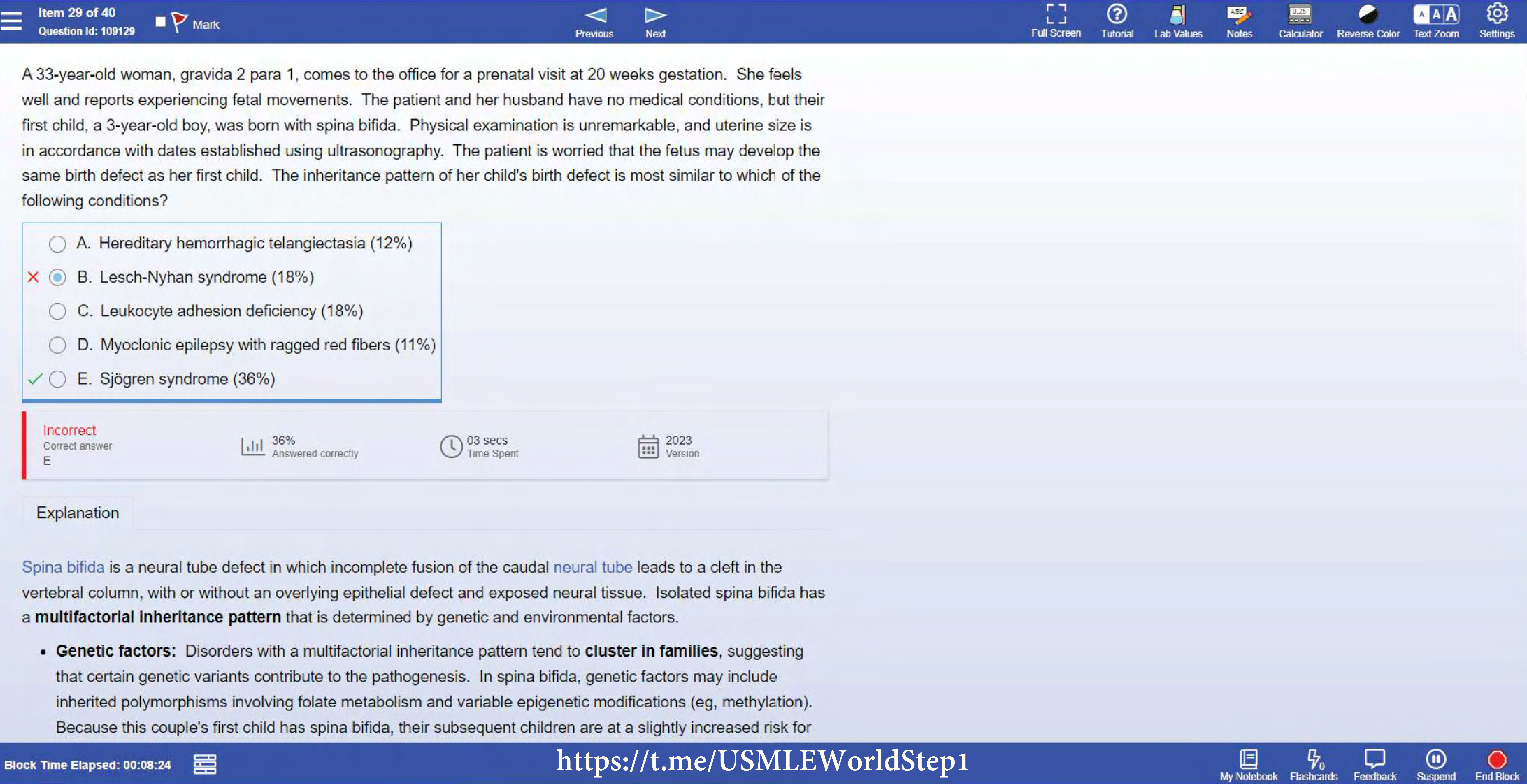
- **Genetic factors:** Disorders with a multifactorial inheritance pattern tend to **cluster in families**, suggesting that certain genetic variants contribute to the pathogenesis. In spina bifida, genetic factors may include inherited polymorphisms involving folate metabolism and variable epigenetic modifications (eg, methylation). Because this couple's first child has spina bifida, their subsequent children are at a slightly increased risk for the condition compared to the general population.
- **Environmental factors:** Maternal **folic acid deficiency** is a preventable risk factor for spina bifida. Similarly, in utero exposure to medications that interfere with folic acid metabolism (eg, valproic acid) is also associated with spina bifida. Other risk factors include maternal obesity and poorly controlled pregestational diabetes mellitus.

Like spina bifida, **Sjögren syndrome** has a multifactorial inheritance pattern. Sjögren syndrome is an autoimmune disorder in which chronic inflammation leads to exocrine gland (eg, salivary, lacrimal) destruction, causing dry eyes and mouth. Although certain genotypes are associated with Sjögren syndrome, environmental factors also determine its incidence. A recent viral illness, for example, can lead to the production of autoantibodies (eg, anti-Ro/SSA, anti-La/SSB) that target exocrine glands.

A multifactorial inheritance pattern is also characteristic of many other birth defects (eg, cleft palate) and autoimmune disorders (eg, type 1 diabetes mellitus) as well as atopic disease (eg, asthma).

(Choice A) Hereditary hemorrhagic telangiectasia is characterized by development of multiple arteriovenous malformations (absent capillary beds). It is inherited in an autosomal dominant pattern rather than a multifactorial inheritance pattern.

(Choice B) Lesch-Nyhan syndrome is characterized by impaired purine salvage resulting in neurobehavioral symptoms (eg, developmental delay, self-mutilating behavior). This condition is inherited in an X-linked recessive pattern.


Item 29 of 40
Question Id: 109129
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient and her husband have no medical conditions, but their first child, a 3-year-old boy, was born with spina bifida. Physical examination is unremarkable, and uterine size is in accordance with dates established using ultrasonography. The patient is worried that the fetus may develop the same birth defect as her first child. The inheritance pattern of her child's birth defect is most similar to which of the following conditions?

○ A. Hereditary hemorrhagic telangiectasia (12%)
✗ ● B. Lesch-Nyhan syndrome (18%)
○ C. Leukocyte adhesion deficiency (18%)
○ D. Myoclonic epilepsy with ragged red fibers (11%)
✓ ○ E. Sjögren syndrome (36%)

Incorrect
Correct answer
E

36%
Answered correctly

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2023
Version

Explanation

Spina bifida is a neural tube defect in which incomplete fusion of the caudal neural tube leads to a cleft in the vertebral column, with or without an overlying epithelial defect and exposed neural tissue. Isolated spina bifida has a **multifactorial inheritance pattern** that is determined by genetic and environmental factors.

- **Genetic factors:** Disorders with a multifactorial inheritance pattern tend to **cluster in families**, suggesting that certain genetic variants contribute to the pathogenesis. In spina bifida, genetic factors may include inherited polymorphisms involving folate metabolism and variable epigenetic modifications (eg, methylation). Because this couple's first child has spina bifida, their subsequent children are at a slightly increased risk for

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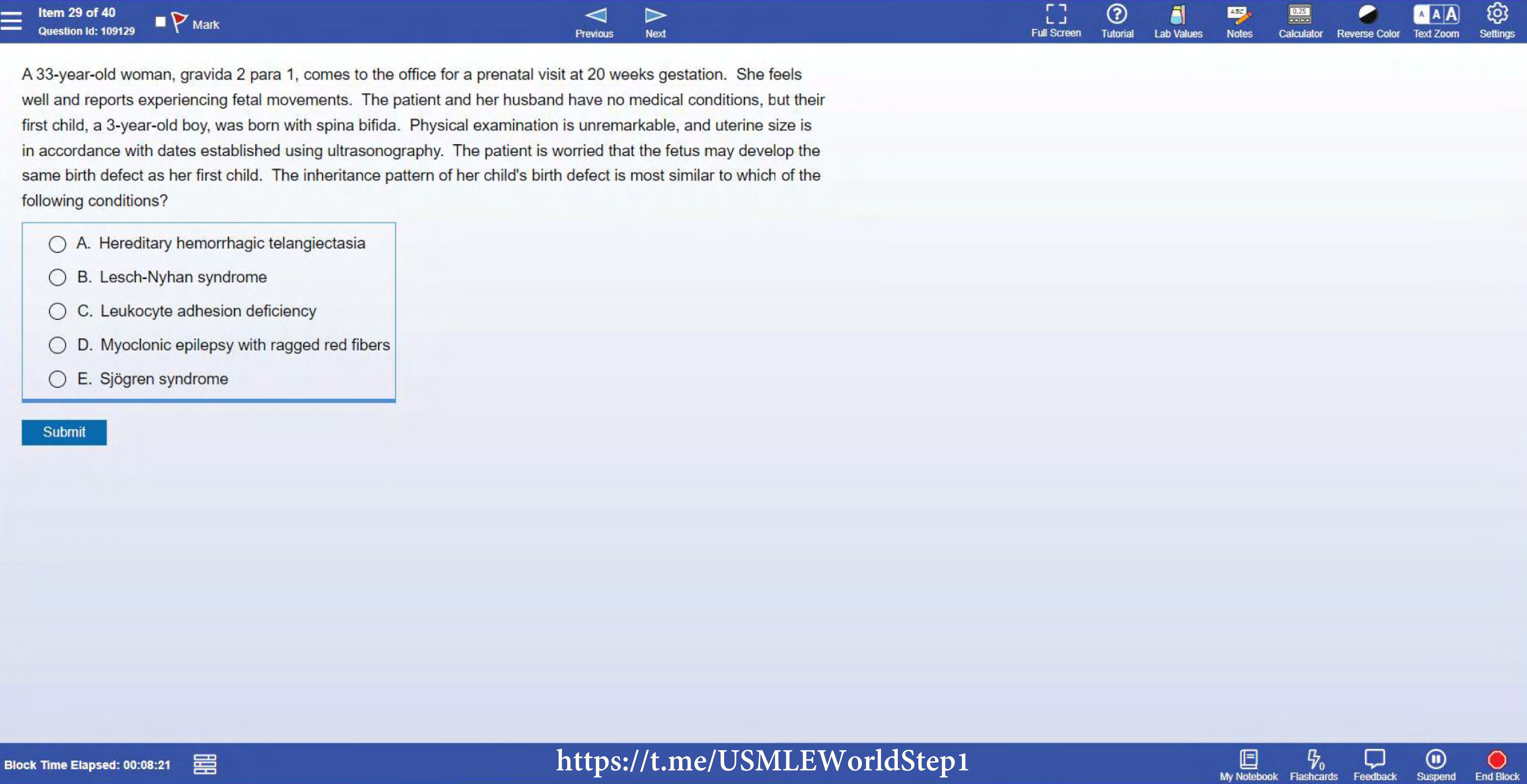
My Notebook
Flashcards
Feedback
Suspend
End Block


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 29 of 40
Question Id: 109129

A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient and her husband have no medical conditions, but their first child, a 3-year-old boy, was born with spina bifida. Physical examination is unremarkable, and uterine size is in accordance with dates established using ultrasonography. The patient is worried that the fetus may develop the same birth defect as her first child. The inheritance pattern of her child's birth defect is most similar to which of the following conditions?

○ A. Hereditary hemorrhagic telangiectasia
○ B. Lesch-Nyhan syndrome
○ C. Leukocyte adhesion deficiency
○ D. Myoclonic epilepsy with ragged red fibers
○ E. Sjögren syndrome

Block Time Elapsed: 00:08:21

Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:08:21
My Notebook
Flashcards
Feedback
Suspend
End Block

of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA tail**, which is added to the **3'** end of tRNA as a post-transcriptional modification and serves as the **amino acid binding site**. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice B) The T loop contains the TΨC sequence, which is necessary for the binding of tRNA to ribosomes. The TΨC sequence refers to the presence of the chemically modified bases ribothymidine and pseudouridine, and cytidine.

(Choice C) The variable loop contains a variable number of bases that lie between the T and anticodon loops. The variable loop is not present in all tRNAs.

(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid in the growing polypeptide chain.

(Choice E) The D loop contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice F) The 5' end of tRNA contains a terminal phosphate group that does not participate in amino acid or mRNA binding.

Educational objective:

The 3' CCA tail of tRNA serves as the amino acid binding site. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail.

References

- CCA addition to tRNA: implications for tRNA quality control.

Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Anticodon loop
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Block Time Elapsed: 00:08:21
My Notebook
Flashcards
Feedback
Suspend
End Block

The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA tail**, which is added to the **3'** end of tRNA as a post-transcriptional modification and serves as the **amino acid binding site**. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice B) The T loop contains the TΨC sequence, which is necessary for the binding of tRNA to ribosomes. The TΨC sequence refers to the presence of the chemically modified bases ribothymidine and pseudouridine, and cytidine.

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(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid in the growing polypeptide chain.

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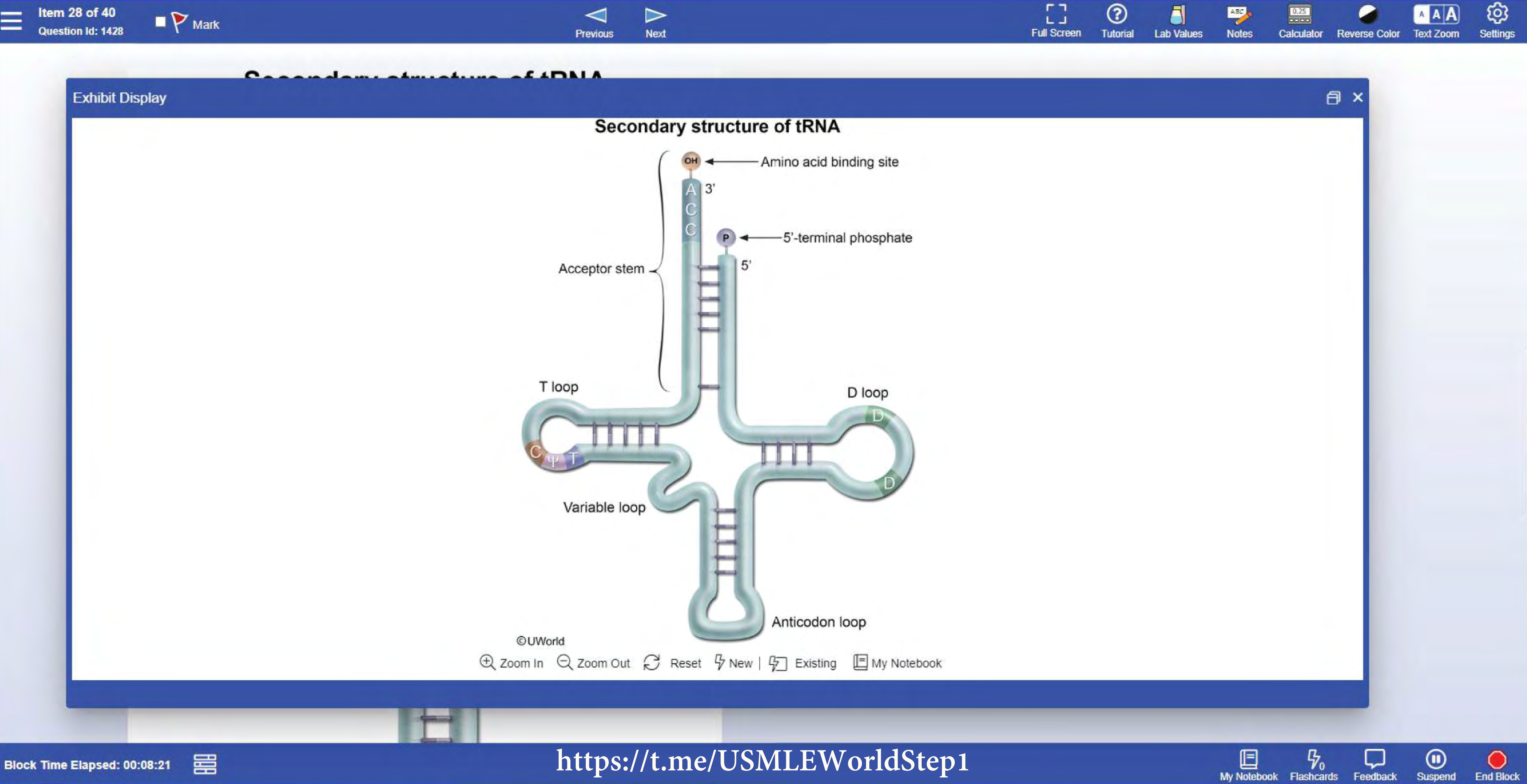
(Choice F) The 5' end of tRNA contains a terminal phosphate group that does not participate in amino acid or mRNA binding.

Educational objective:

The 3' CCA tail of tRNA serves as the amino acid binding site. Aminoacyl tRNA synthetase is the enzyme


Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display

Secondary structure of tRNA

OH
Amino acid binding site
A
C
C
3'
P
5'-terminal phosphate
5'
Acceptor stem
T loop
C
Ψ
T
D loop
D
D
Variable loop
Anticodon loop

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My Notebook
Block Time Elapsed: 00:08:21
My Notebook
Flashcards
Feedback
Suspend
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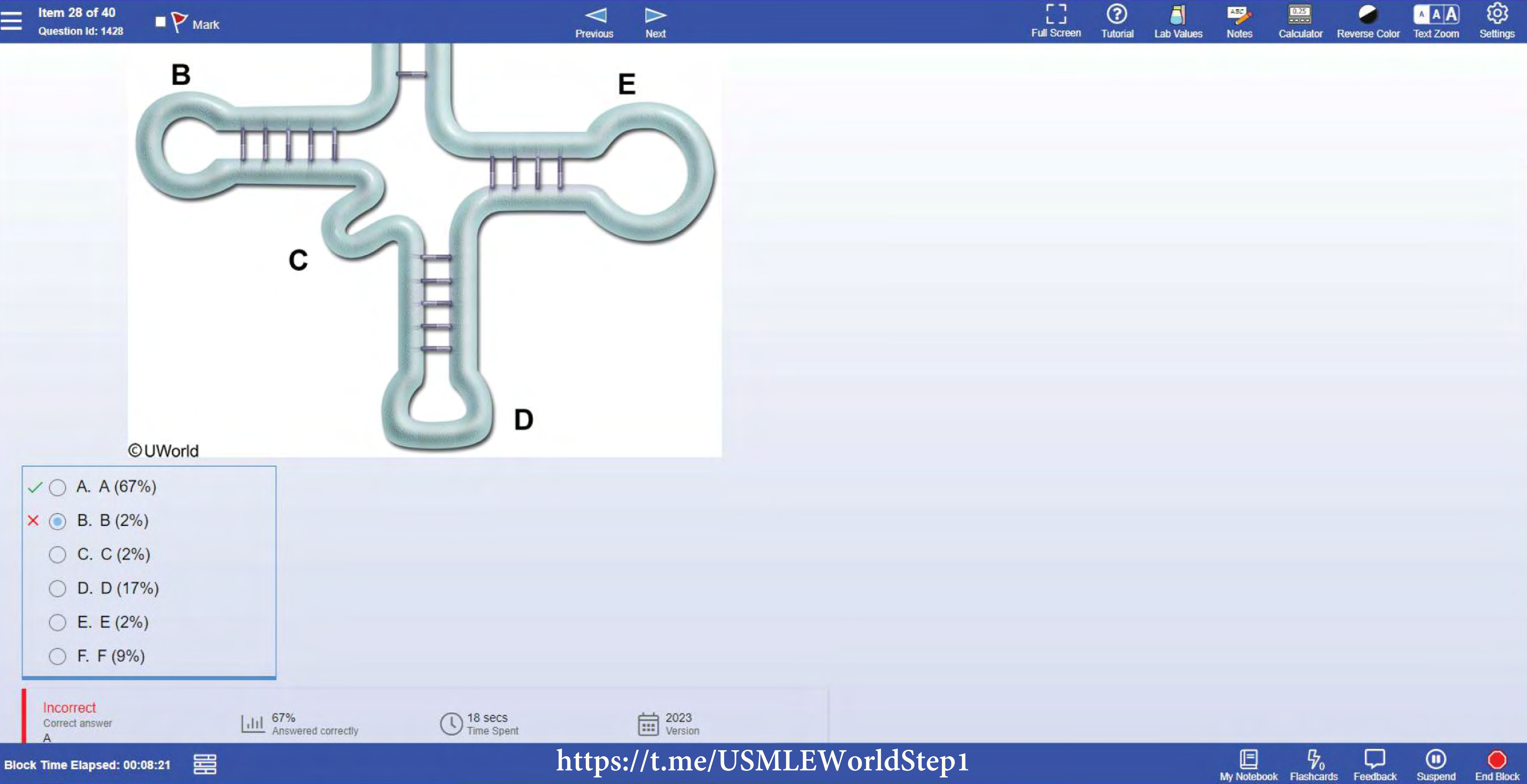
Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
B
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©UWorld
My Notebook
Flashcards
Feedback
Suspend
End Block

✓ ○ A. A (67%)

✗ ● B. B (2%)

○ C. C (2%)

○ D. D (17%)

○ E. E (2%)

○ F. F (9%)

Incorrect
Correct answer
A

67%
Answered correctly

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2023
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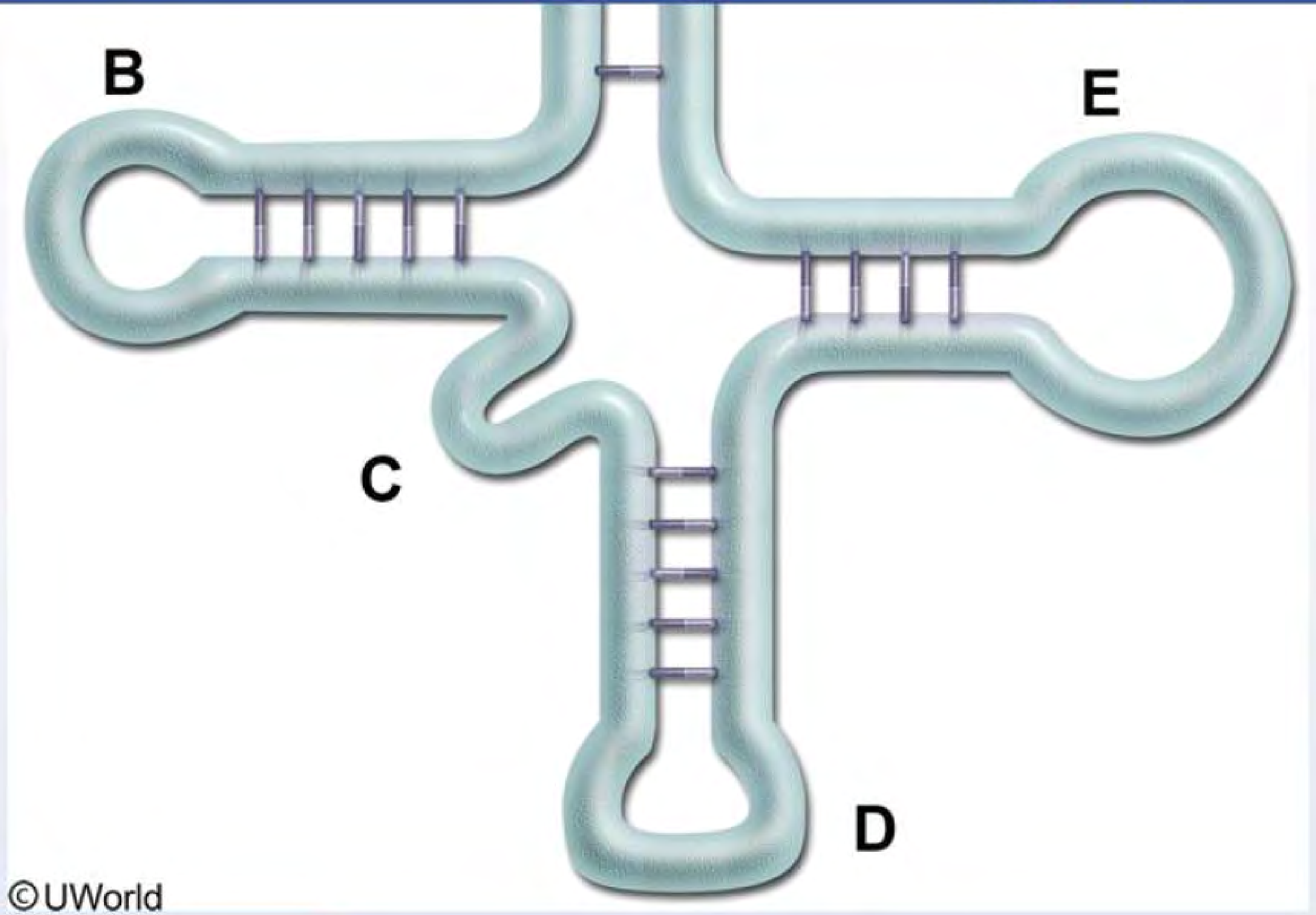
Block Time Elapsed: 00:08:21



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○ A. A

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○ F. F

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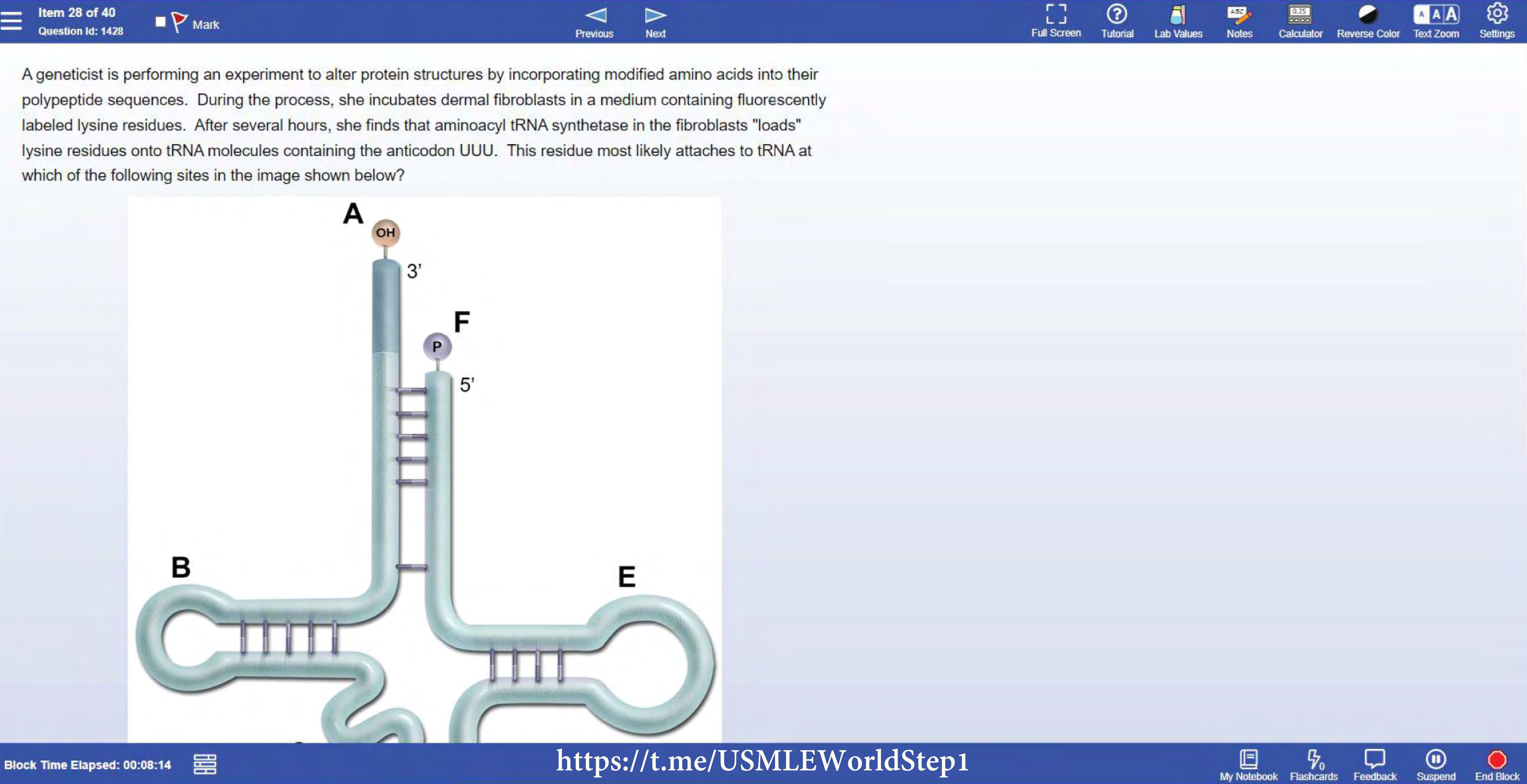

Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?

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My Notebook
Flashcards
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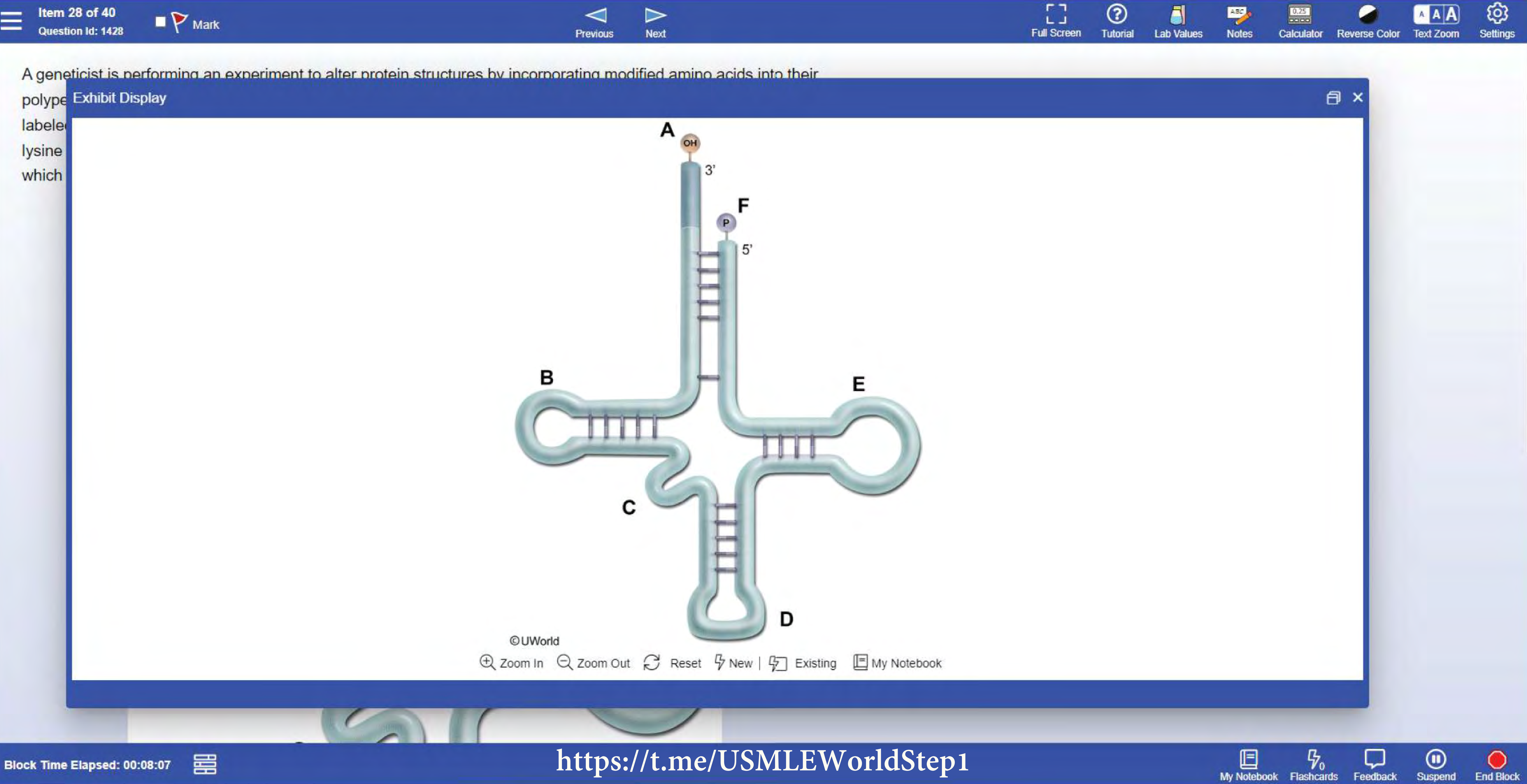
Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
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A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their

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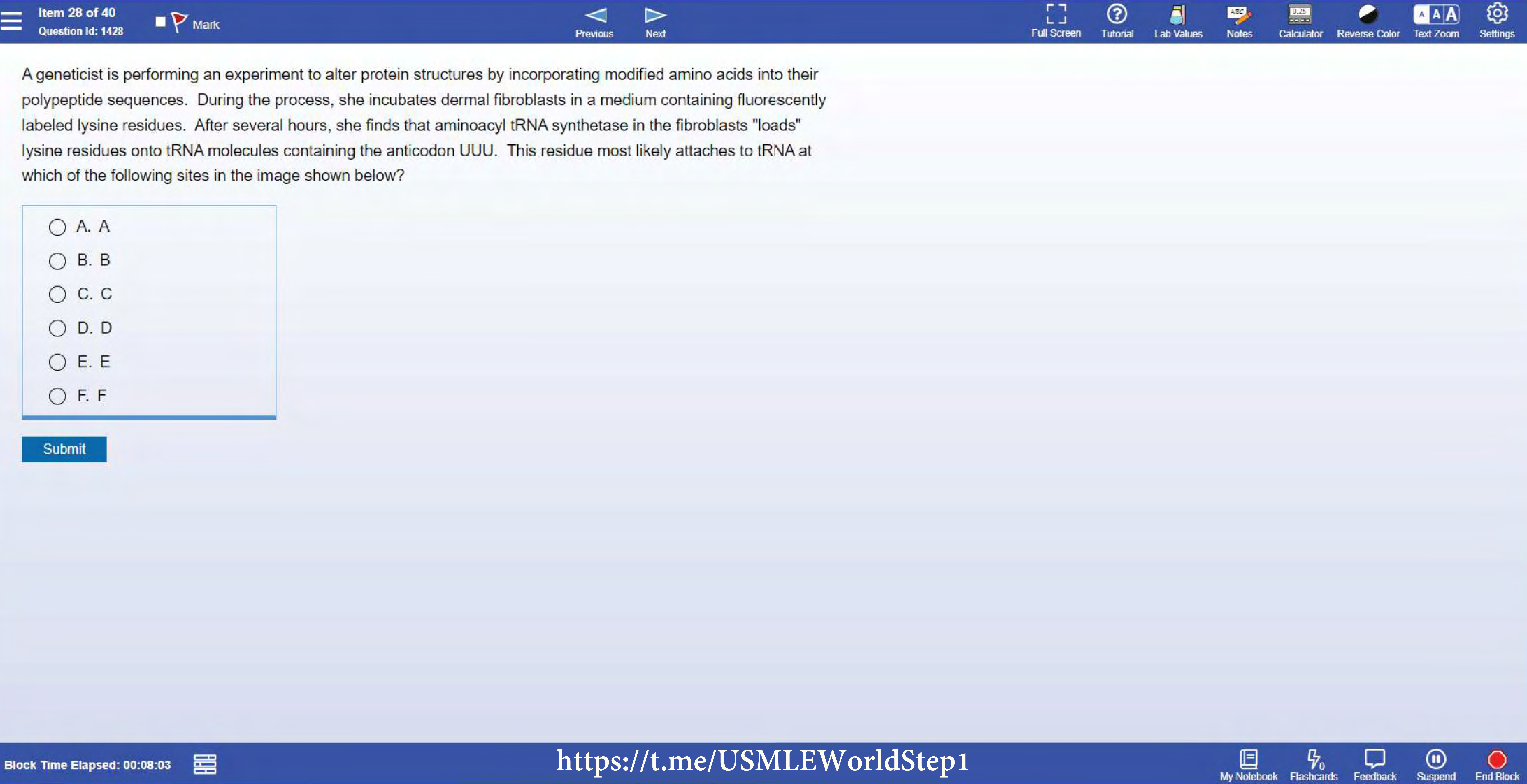
Item 28 of 40
Question Id: 1428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. A
○ B. B
○ C. C
○ D. D
○ E. E
○ F. F

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Flashcards
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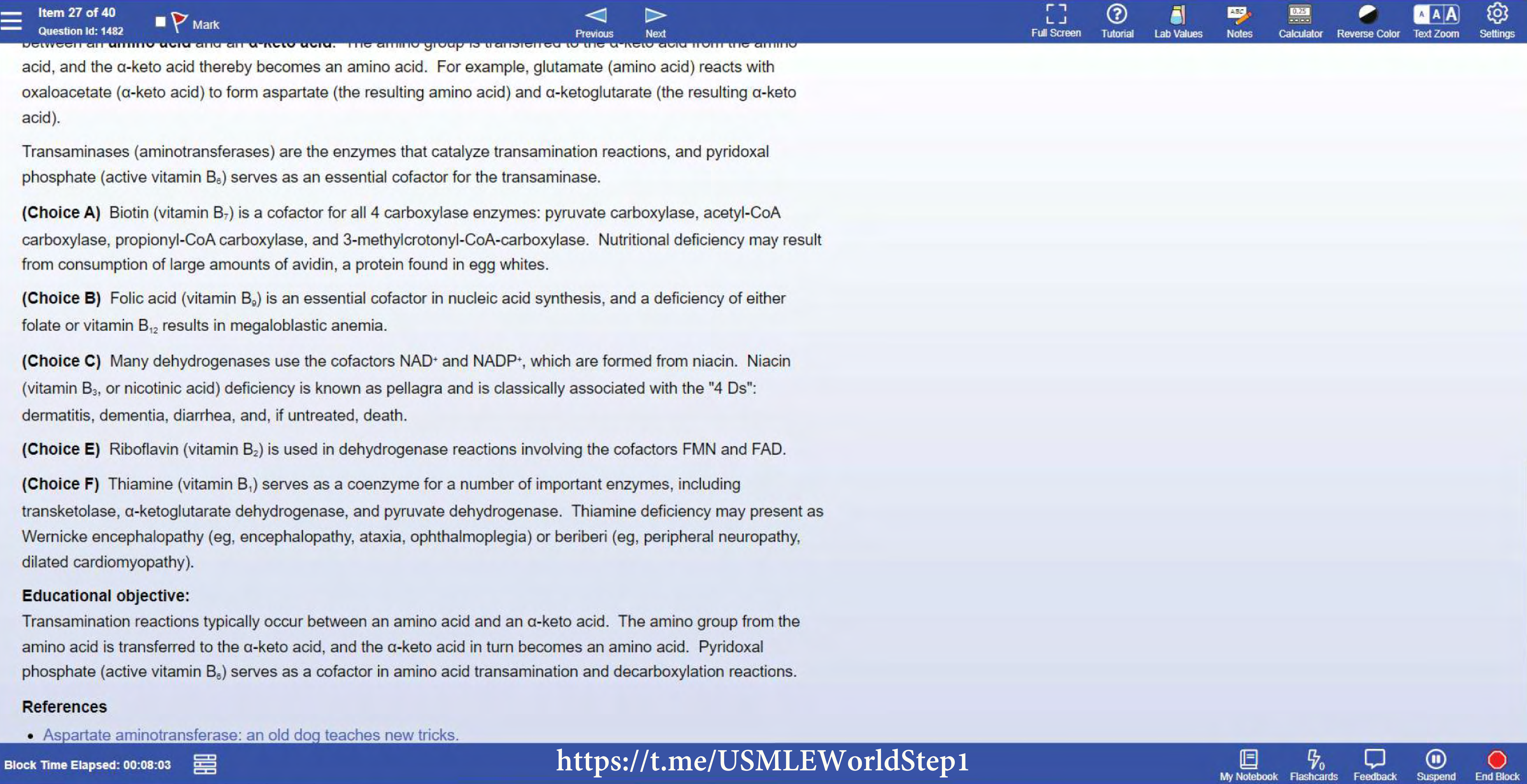


between an **amino acid** and an **α-keto acid**. The amino group is transferred to the α-keto acid from the amino acid, and the α-keto acid thereby becomes an amino acid. For example, glutamate (amino acid) reacts with oxaloacetate (α-keto acid) to form aspartate (the resulting amino acid) and α-ketoglutarate (the resulting α-keto acid).

Transaminases (aminotransferases) are the enzymes that catalyze transamination reactions, and pyridoxal phosphate (active vitamin B$_6$) serves as an essential cofactor for the transaminase.

(Choice A) Biotin (vitamin B$_7$) is a cofactor for all 4 carboxylase enzymes: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA-carboxylase. Nutritional deficiency may result from consumption of large amounts of avidin, a protein found in egg whites.

(Choice B) Folic acid (vitamin B$_9$) is an essential cofactor in nucleic acid synthesis, and a deficiency of either folate or vitamin B$_{12}$ results in megaloblastic anemia.

(Choice C) Many dehydrogenases use the cofactors NAD$^+$ and NADP$^+$, which are formed from niacin. Niacin (vitamin B$_3$, or nicotinic acid) deficiency is known as pellagra and is classically associated with the "4 Ds": dermatitis, dementia, diarrhea, and, if untreated, death.

(Choice E) Riboflavin (vitamin B$_2$) is used in dehydrogenase reactions involving the cofactors FMN and FAD.

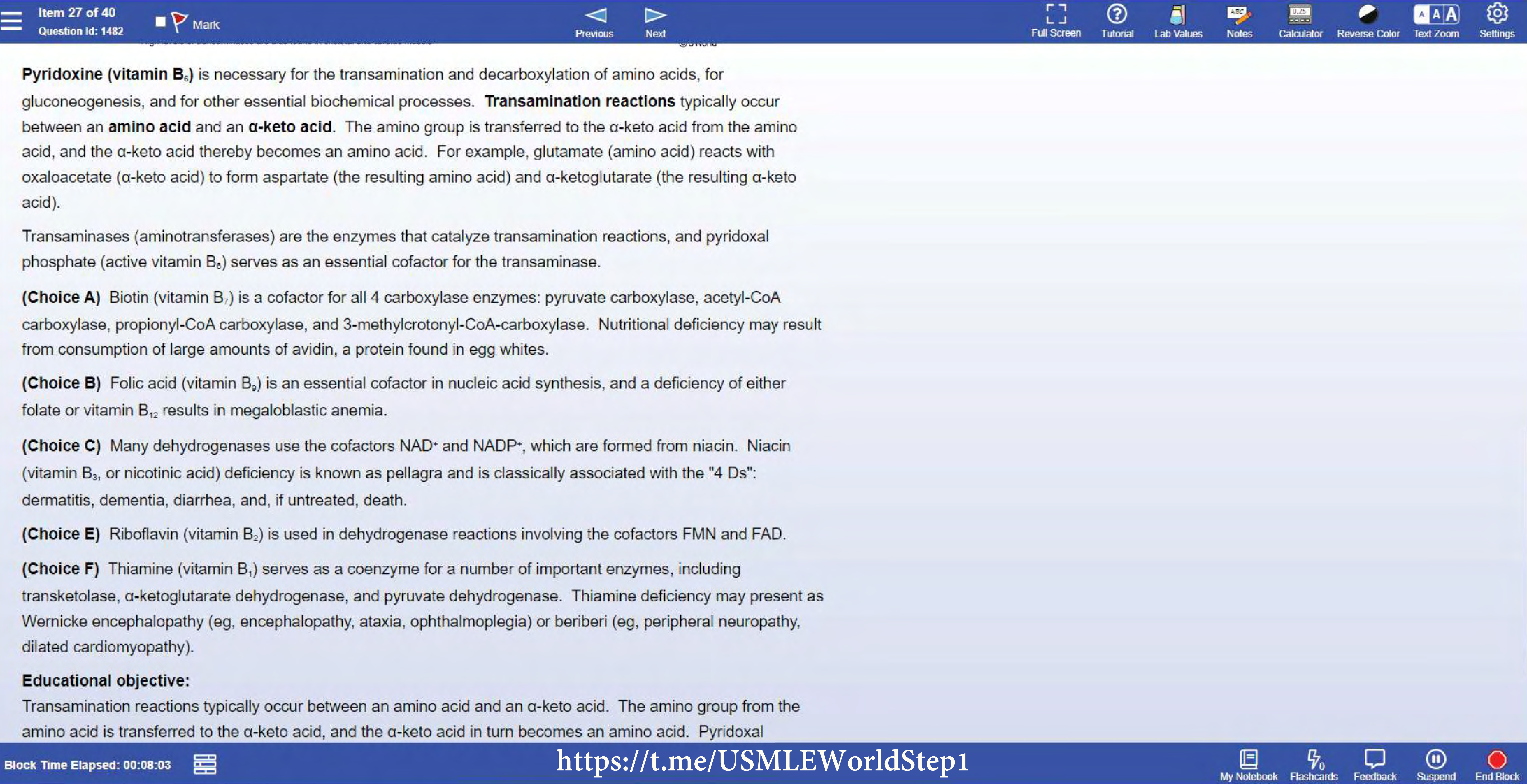
(Choice F) Thiamine (vitamin B$_1$) serves as a coenzyme for a number of important enzymes, including transketolase, α-ketoglutarate dehydrogenase, and pyruvate dehydrogenase. Thiamine deficiency may present as Wernicke encephalopathy (eg, encephalopathy, ataxia, ophthalmoplegia) or beriberi (eg, peripheral neuropathy, dilated cardiomyopathy).

Educational objective:

Transamination reactions typically occur between an amino acid and an α-keto acid. The amino group from the amino acid is transferred to the α-keto acid, and the α-keto acid in turn becomes an amino acid. Pyridoxal phosphate (active vitamin B$_6$) serves as a cofactor in amino acid transamination and decarboxylation reactions.

References

- Aspartate aminotransferase: an old dog teaches new tricks.



Pyridoxine (vitamin B_6) is necessary for the transamination and decarboxylation of amino acids, for gluconeogenesis, and for other essential biochemical processes. **Transamination reactions** typically occur between an **amino acid** and an **α-keto acid**. The amino group is transferred to the α-keto acid from the amino acid, and the α-keto acid thereby becomes an amino acid. For example, glutamate (amino acid) reacts with oxaloacetate (α-keto acid) to form aspartate (the resulting amino acid) and α-ketoglutarate (the resulting α-keto acid).

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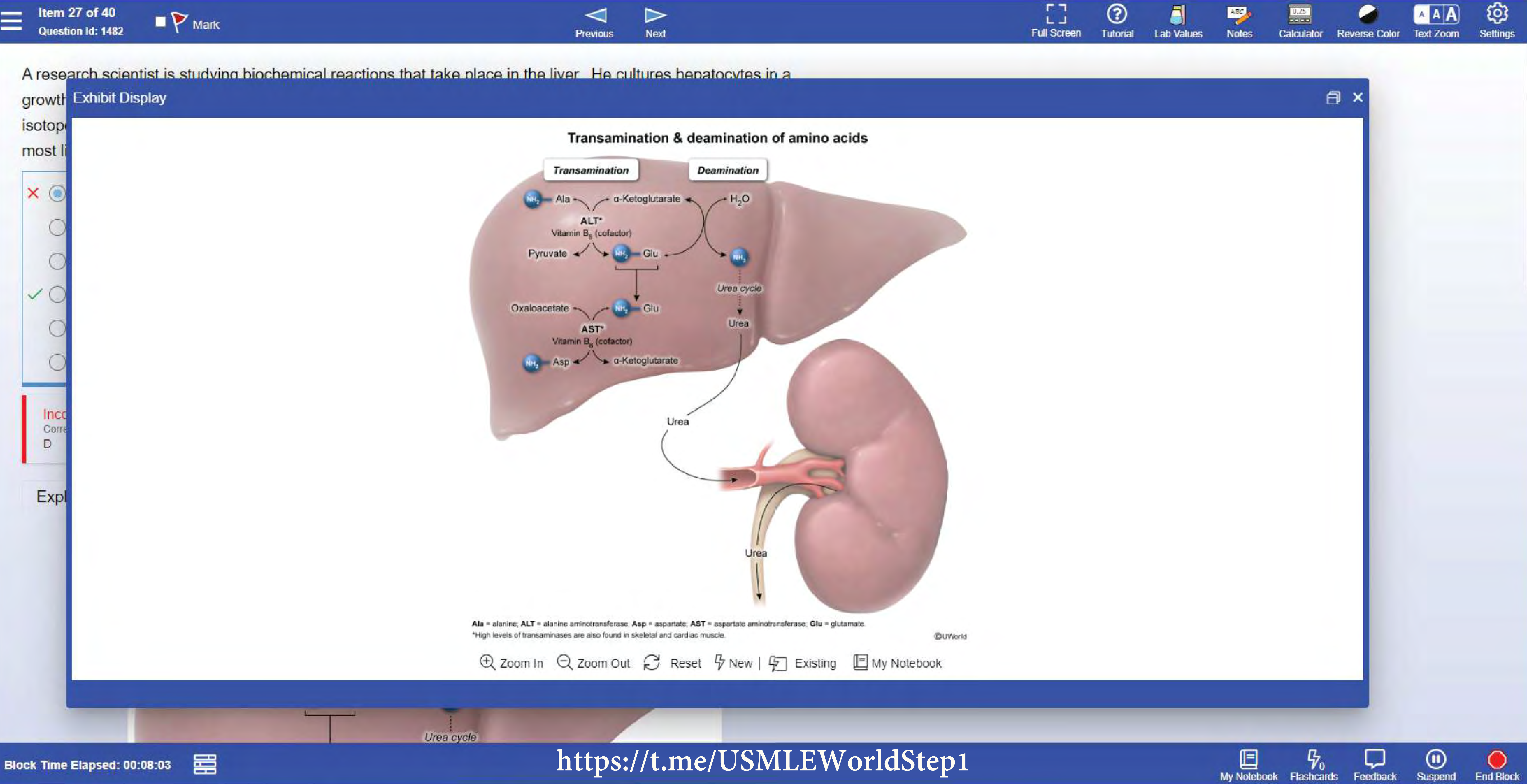
Educational objective:

Transamination reactions typically occur between an amino acid and an α-keto acid. The amino group from the amino acid is transferred to the α-keto acid, and the α-keto acid in turn becomes an amino acid. Pyridoxal


Item 27 of 40
Question Id: 1482
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a

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Transamination & deamination of amino acids

Transamination
Deamination
NH_2
Ala
α-Ketoglutarate
H_2O
ALT*
Vitamin B_6 (cofactor)
Pyruvate
NH_2
Glu
NH_3
Urea cycle
Urea
Oxaloacetate
NH_2
Glu
AST*
Vitamin B_6 (cofactor)
NH_2
Asp
α-Ketoglutarate
Urea
Urea

Ala = alanine; **ALT** = alanine aminotransferase; **Asp** = aspartate; **AST** = aspartate aminotransferase; **Glu** = glutamate.

*High levels of transaminases are also found in skeletal and cardiac muscle.

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Existing
My Notebook
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Block Time Elapsed: 00:08:03

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My Notebook
Flashcards
Feedback
Suspend
End Block

A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a growth media enriched with glutamate labeled with nitrogen isotopes. After some time, he finds that the nitrogen isotopes are transferred to oxaloacetate, forming aspartate in the process. Which of the following substances is most likely involved in this reaction?

- ✗ ● A. Biotin (16%)
- ○ B. Folic acid (3%)
- ○ C. Niacin (17%)
- ✓ ○ D. Pyridoxine (40%)
- ○ E. Riboflavin (7%)
- ○ F. Thiamine (14%)

Incorrect
Correct answer
D

40%
Answered correctly

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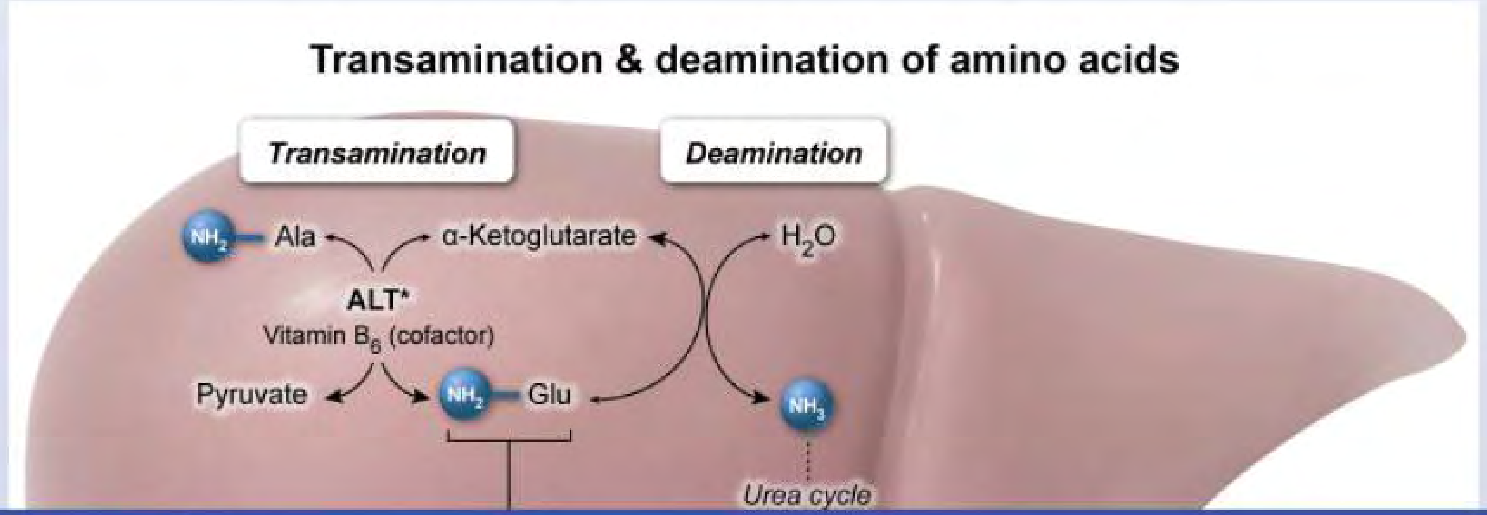
2023
Version

Explanation


Transamination & deamination of amino acids
Transamination
Deamination
NH₂
Ala
α-Ketoglutarate
H₂O
ALT*
Vitamin B₆ (cofactor)
Pyruvate
NH₂
Glu
NH₃
Urea cycle

Item 27 of 40
Question Id: 1482
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a growth media enriched with glutamate labeled with nitrogen isotopes. After some time, he finds that the nitrogen isotopes are transferred to oxaloacetate, forming aspartate in the process. Which of the following substances is most likely involved in this reaction?

- ○ A. Biotin
- ○ B. Folic acid
- ○ C. Niacin
- ○ D. Pyridoxine
- ○ E. Riboflavin
- ○ F. Thiamine

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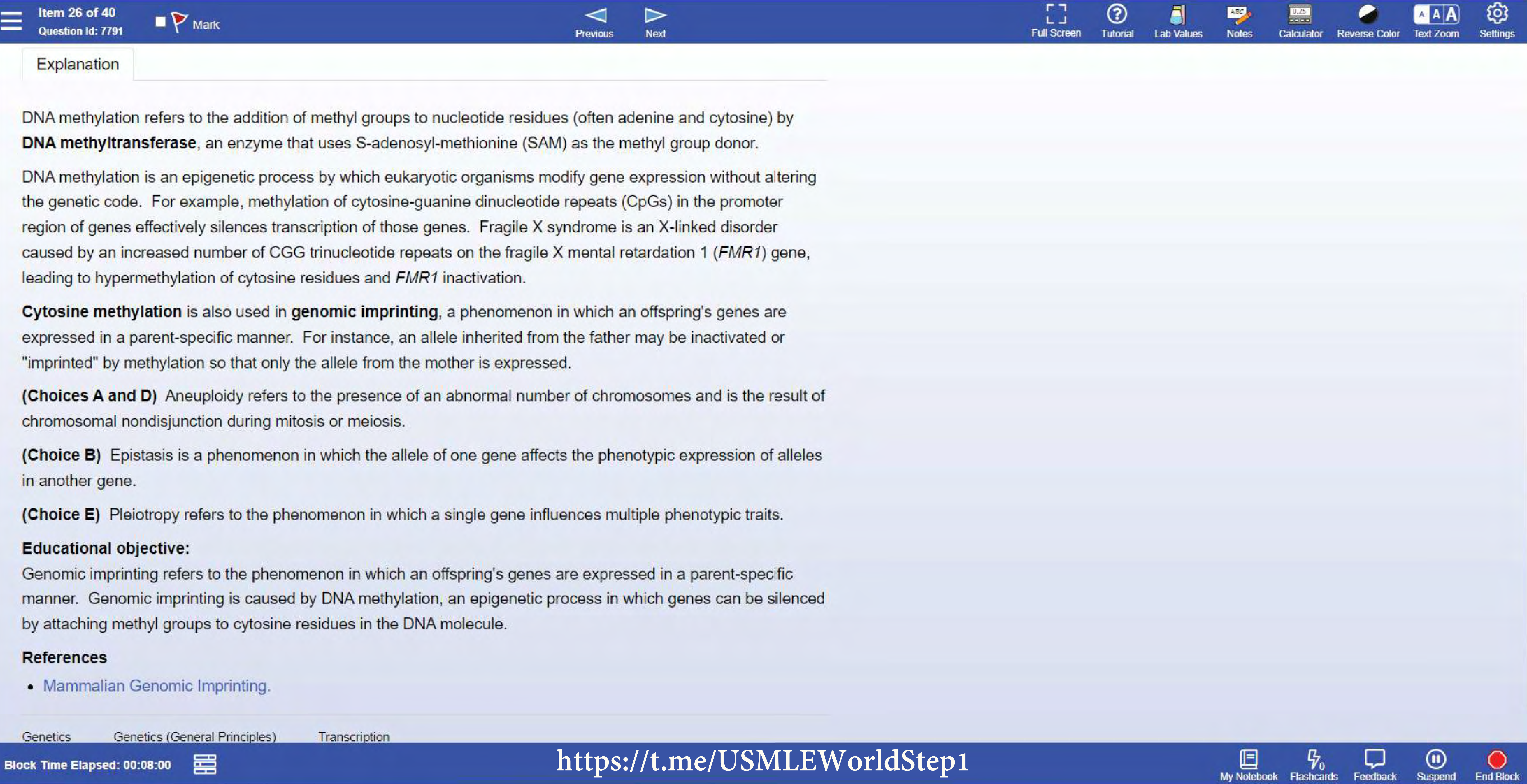
Block Time Elapsed: 00:08:01
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 26 of 40
Question Id: 7791
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

DNA methylation refers to the addition of methyl groups to nucleotide residues (often adenine and cytosine) by **DNA methyltransferase**, an enzyme that uses S-adenosyl-methionine (SAM) as the methyl group donor.

DNA methylation is an epigenetic process by which eukaryotic organisms modify gene expression without altering the genetic code. For example, methylation of cytosine-guanine dinucleotide repeats (CpGs) in the promoter region of genes effectively silences transcription of those genes. Fragile X syndrome is an X-linked disorder caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1 (*FMR1*) gene, leading to hypermethylation of cytosine residues and *FMR1* inactivation.

Cytosine methylation is also used in **genomic imprinting**, a phenomenon in which an offspring's genes are expressed in a parent-specific manner. For instance, an allele inherited from the father may be inactivated or "imprinted" by methylation so that only the allele from the mother is expressed.

(Choices A and D) Aneuploidy refers to the presence of an abnormal number of chromosomes and is the result of chromosomal nondisjunction during mitosis or meiosis.

(Choice B) Epistasis is a phenomenon in which the allele of one gene affects the phenotypic expression of alleles in another gene.

(Choice E) Pleiotropy refers to the phenomenon in which a single gene influences multiple phenotypic traits.

Educational objective:
Genomic imprinting refers to the phenomenon in which an offspring's genes are expressed in a parent-specific manner. Genomic imprinting is caused by DNA methylation, an epigenetic process in which genes can be silenced by attaching methyl groups to cytosine residues in the DNA molecule.

References

- Mammalian Genomic Imprinting.

Genetics Genetics (General Principles) Transcription

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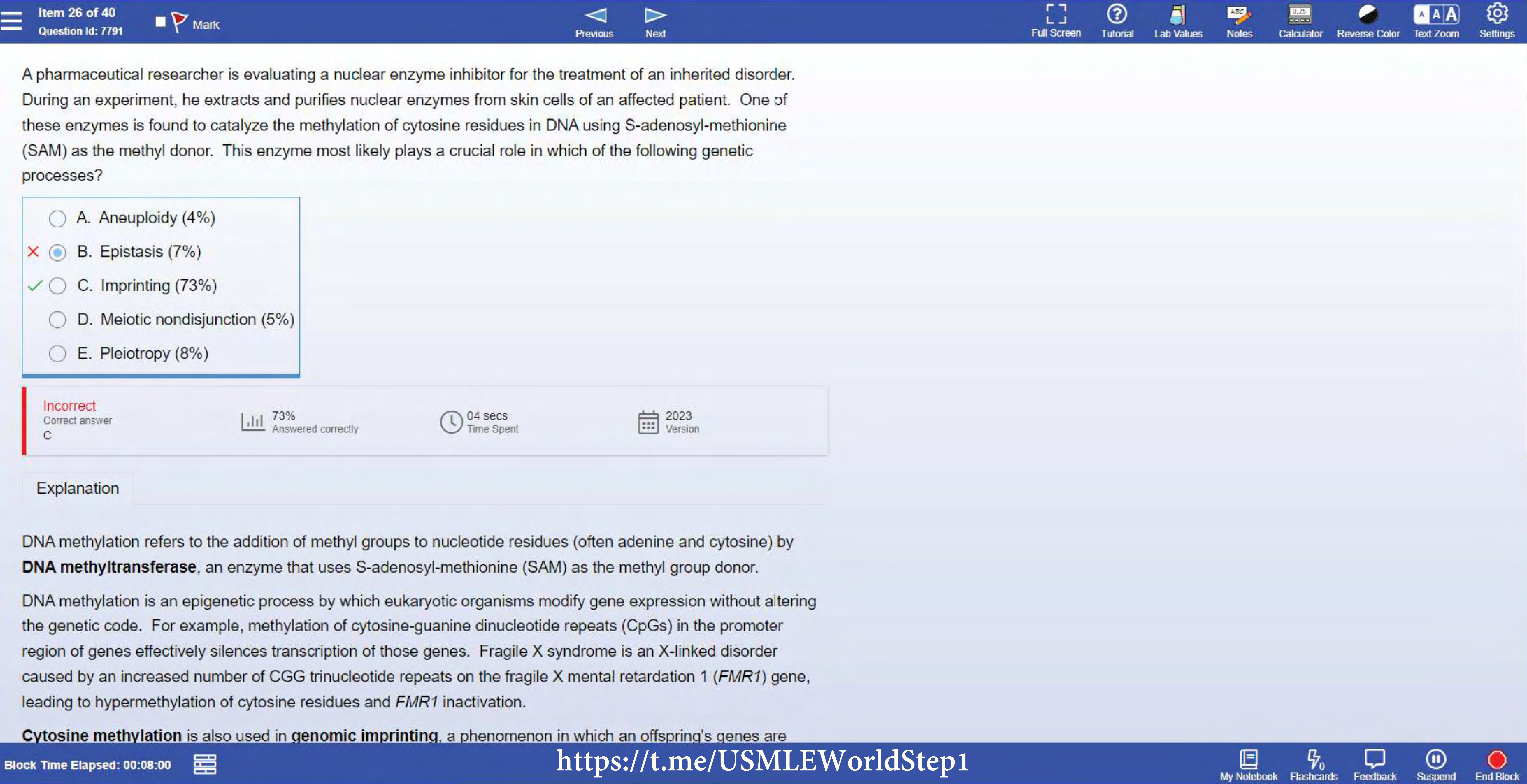
Item 26 of 40
Question Id: 7791
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical researcher is evaluating a nuclear enzyme inhibitor for the treatment of an inherited disorder. During an experiment, he extracts and purifies nuclear enzymes from skin cells of an affected patient. One of these enzymes is found to catalyze the methylation of cytosine residues in DNA using S-adenosyl-methionine (SAM) as the methyl donor. This enzyme most likely plays a crucial role in which of the following genetic processes?

- ○ A. Aneuploidy (4%)
- ✗ ● B. Epistasis (7%)
- ✓ ○ C. Imprinting (73%)
- ○ D. Meiotic nondisjunction (5%)
- ○ E. Pleiotropy (8%)

Incorrect
Correct answer
C

73%
Answered correctly

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Explanation

DNA methylation refers to the addition of methyl groups to nucleotide residues (often adenine and cytosine) by **DNA methyltransferase**, an enzyme that uses S-adenosyl-methionine (SAM) as the methyl group donor.

DNA methylation is an epigenetic process by which eukaryotic organisms modify gene expression without altering the genetic code. For example, methylation of cytosine-guanine dinucleotide repeats (CpGs) in the promoter region of genes effectively silences transcription of those genes. Fragile X syndrome is an X-linked disorder caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1 (*FMR1*) gene, leading to hypermethylation of cytosine residues and *FMR1* inactivation.

Cytosine methylation is also used in **genomic imprinting**, a phenomenon in which an offspring's genes are

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Flashcards
Feedback
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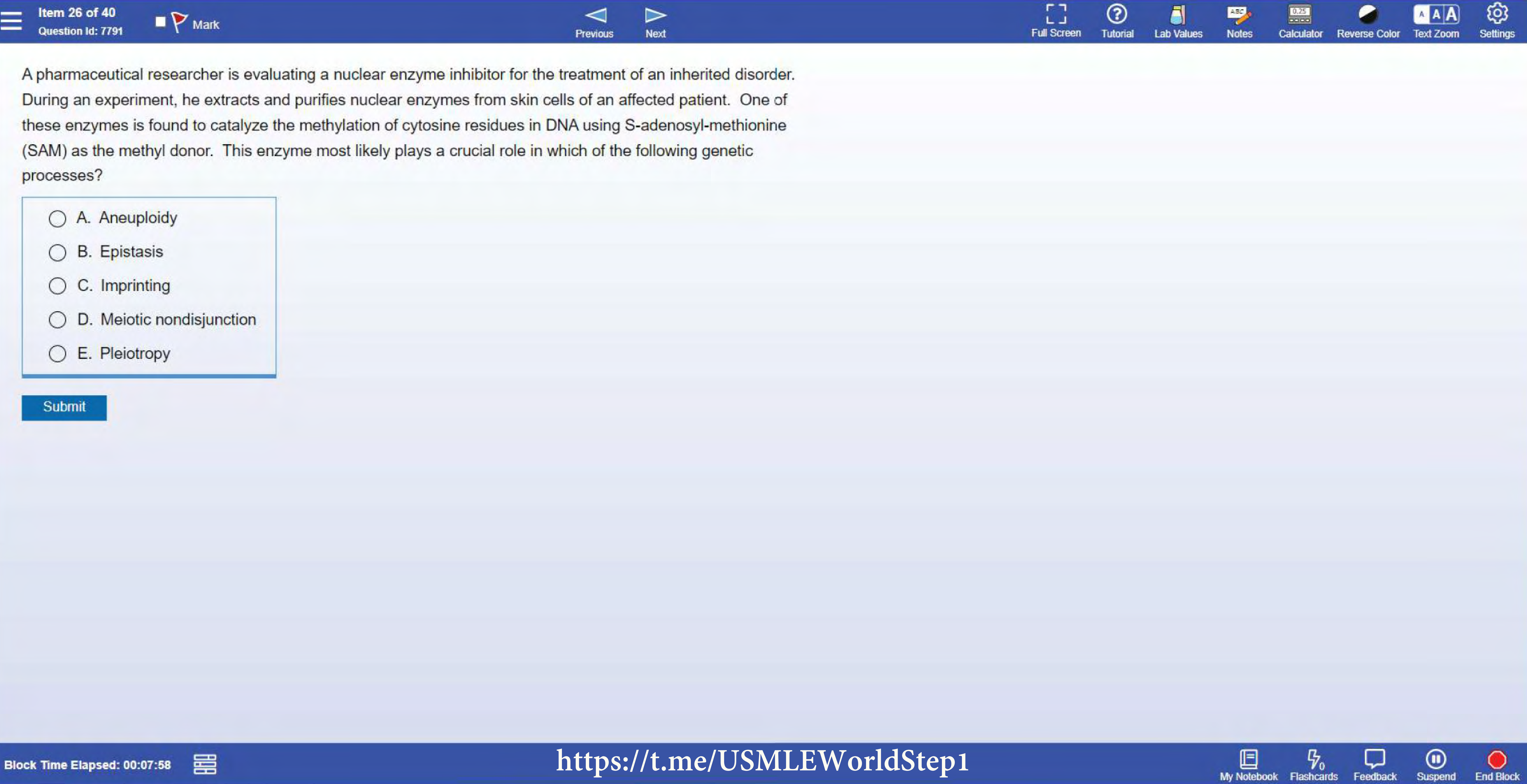
Item 26 of 40
Question Id: 7791
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ A. Aneuploidy
○ B. Epistasis
○ C. Imprinting
○ D. Meiotic nondisjunction
○ E. Pleiotropy

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Genetic information flows from DNA to RNA to proteins. Most eukaryotic DNA sequences consist of coding exons,

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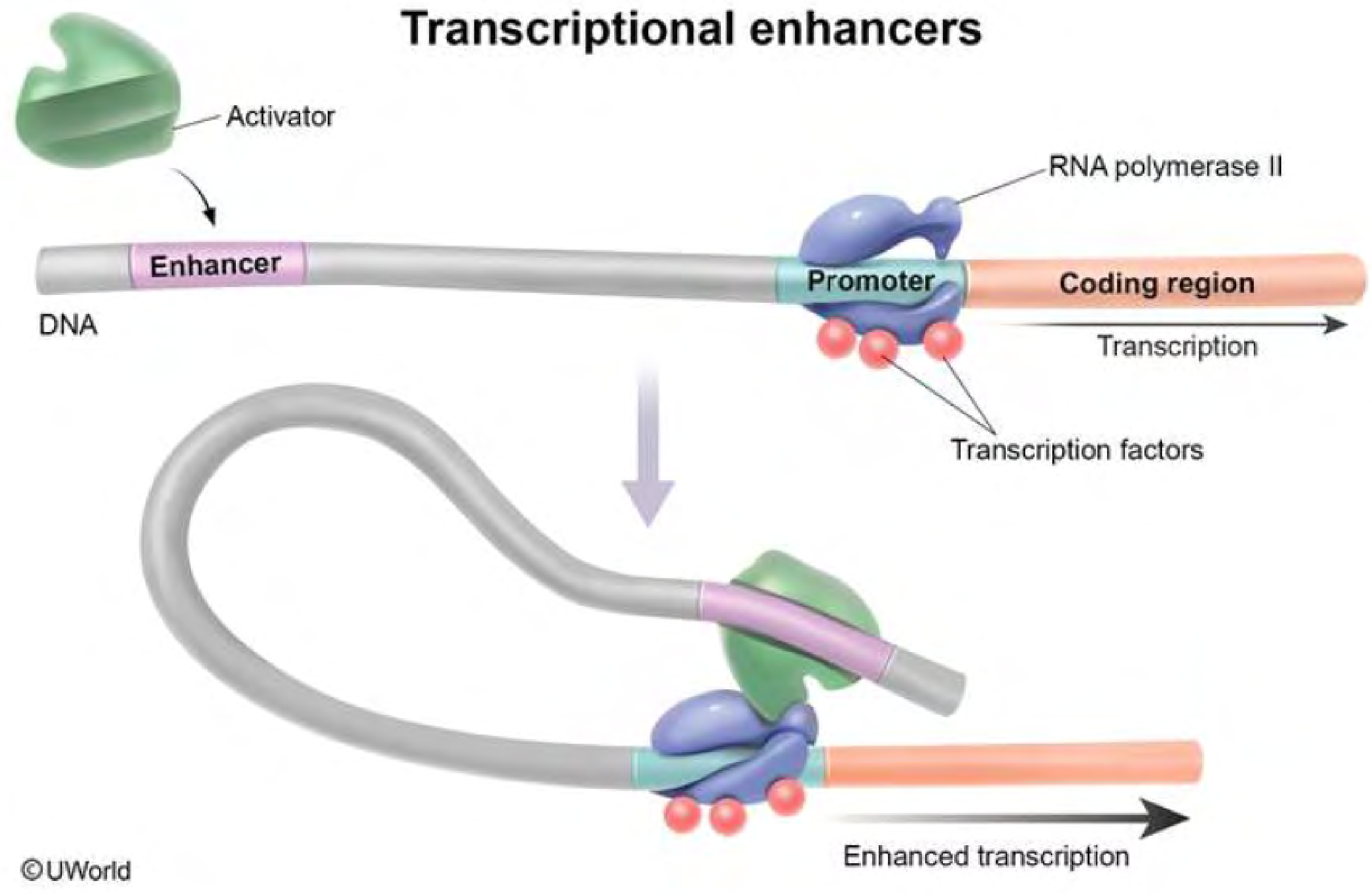
Activator
RNA polymerase II
Enhancer
Promoter
Coding region
DNA
Transcription
Transcription factors
Enhanced transcription

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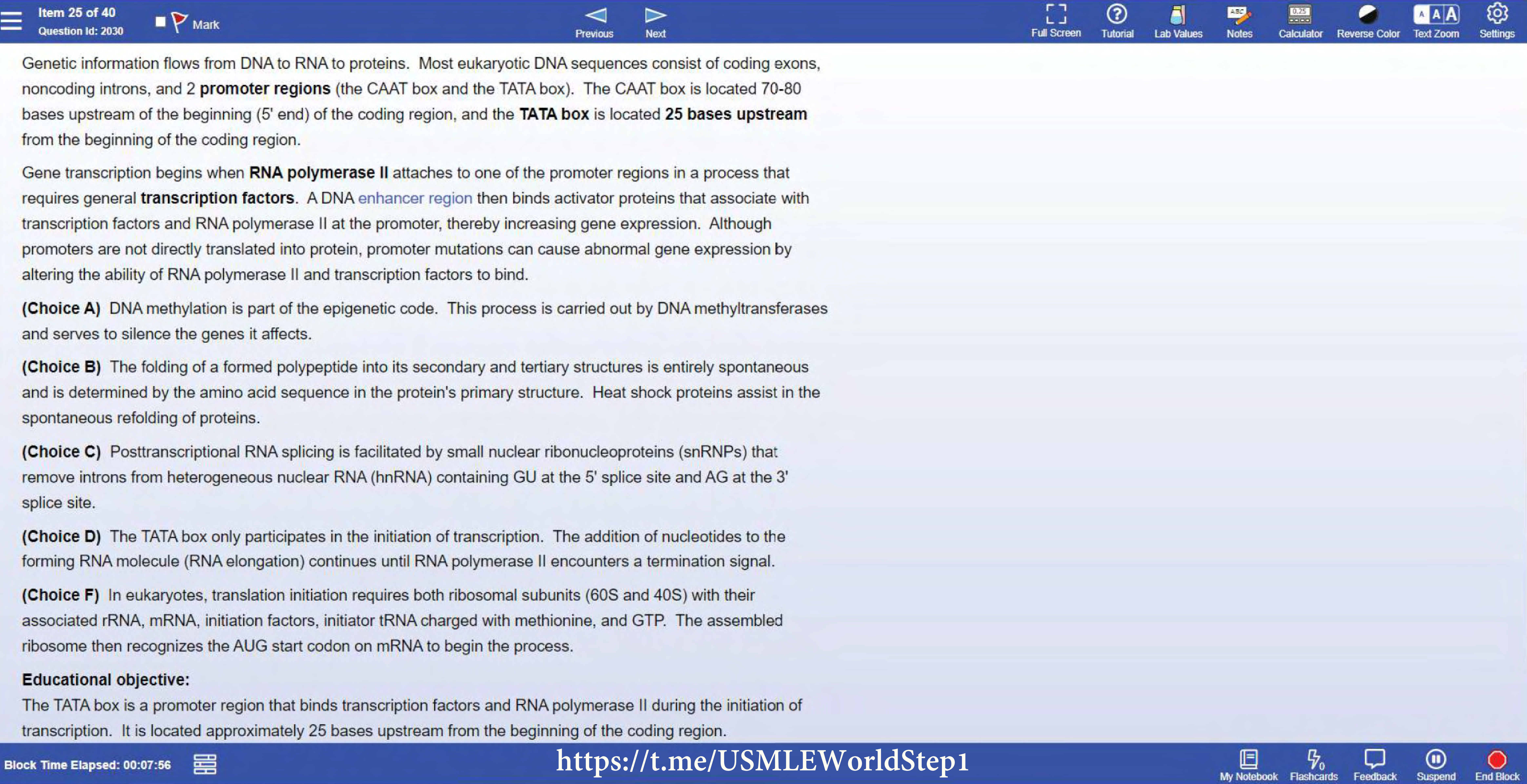
Educational objective:

The TATA box is a promoter region that binds transcription factors and RNA polymerase II during the initiation of transcription. It is located approximately 25 bases upstream from the beginning of the coding region.



Genetic information flows from DNA to RNA to proteins. Most eukaryotic DNA sequences consist of coding exons, noncoding introns, and 2 **promoter regions** (the CAAT box and the TATA box). The CAAT box is located 70-80 bases upstream of the beginning (5' end) of the coding region, and the **TATA box** is located **25 bases upstream** from the beginning of the coding region.

Gene transcription begins when **RNA polymerase II** attaches to one of the promoter regions in a process that requires general **transcription factors**. A DNA enhancer region then binds activator proteins that associate with transcription factors and RNA polymerase II at the promoter, thereby increasing gene expression. Although promoters are not directly translated into protein, promoter mutations can cause abnormal gene expression by altering the ability of RNA polymerase II and transcription factors to bind.

(Choice A) DNA methylation is part of the epigenetic code. This process is carried out by DNA methyltransferases and serves to silence the genes it affects.

(Choice B) The folding of a formed polypeptide into its secondary and tertiary structures is entirely spontaneous and is determined by the amino acid sequence in the protein's primary structure. Heat shock proteins assist in the spontaneous refolding of proteins.

(Choice C) Posttranscriptional RNA splicing is facilitated by small nuclear ribonucleoproteins (snRNPs) that remove introns from heterogeneous nuclear RNA (hnRNA) containing GU at the 5' splice site and AG at the 3' splice site.

(Choice D) The TATA box only participates in the initiation of transcription. The addition of nucleotides to the forming RNA molecule (RNA elongation) continues until RNA polymerase II encounters a termination signal.

(Choice F) In eukaryotes, translation initiation requires both ribosomal subunits (60S and 40S) with their associated rRNA, mRNA, initiation factors, initiator tRNA charged with methionine, and GTP. The assembled ribosome then recognizes the AUG start codon on mRNA to begin the process.

Educational objective:

The TATA box is a promoter region that binds transcription factors and RNA polymerase II during the initiation of transcription. It is located approximately 25 bases upstream from the beginning of the coding region.

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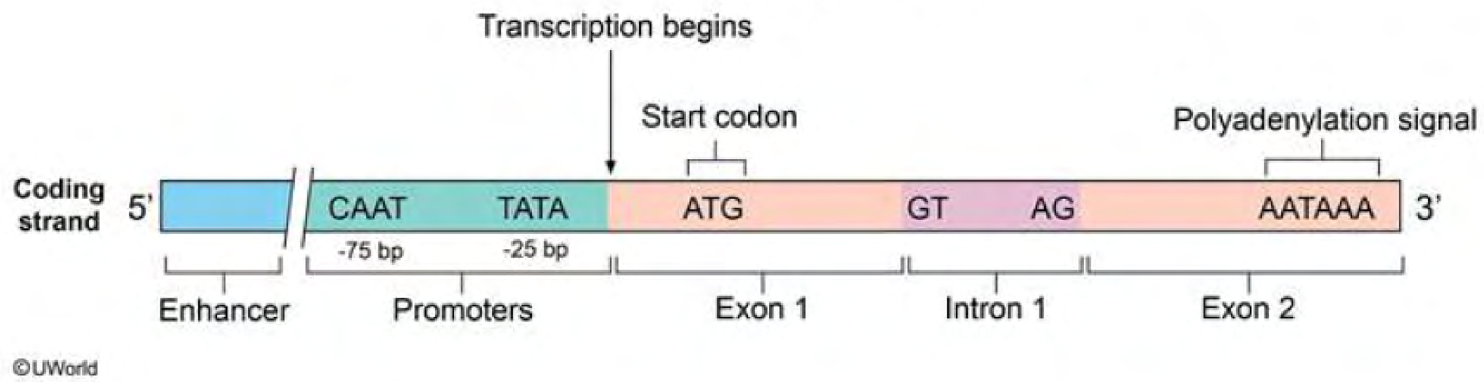
Eukaryotic gene organization


Transcription begins
Start codon
Polyadenylation signal
Coding strand
5'
CAAT
TATA
ATG
GT
AG
AATAAA
3'
-75 bp
-25 bp
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Exon 1
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Exon 2

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spontaneous refolding of proteins.

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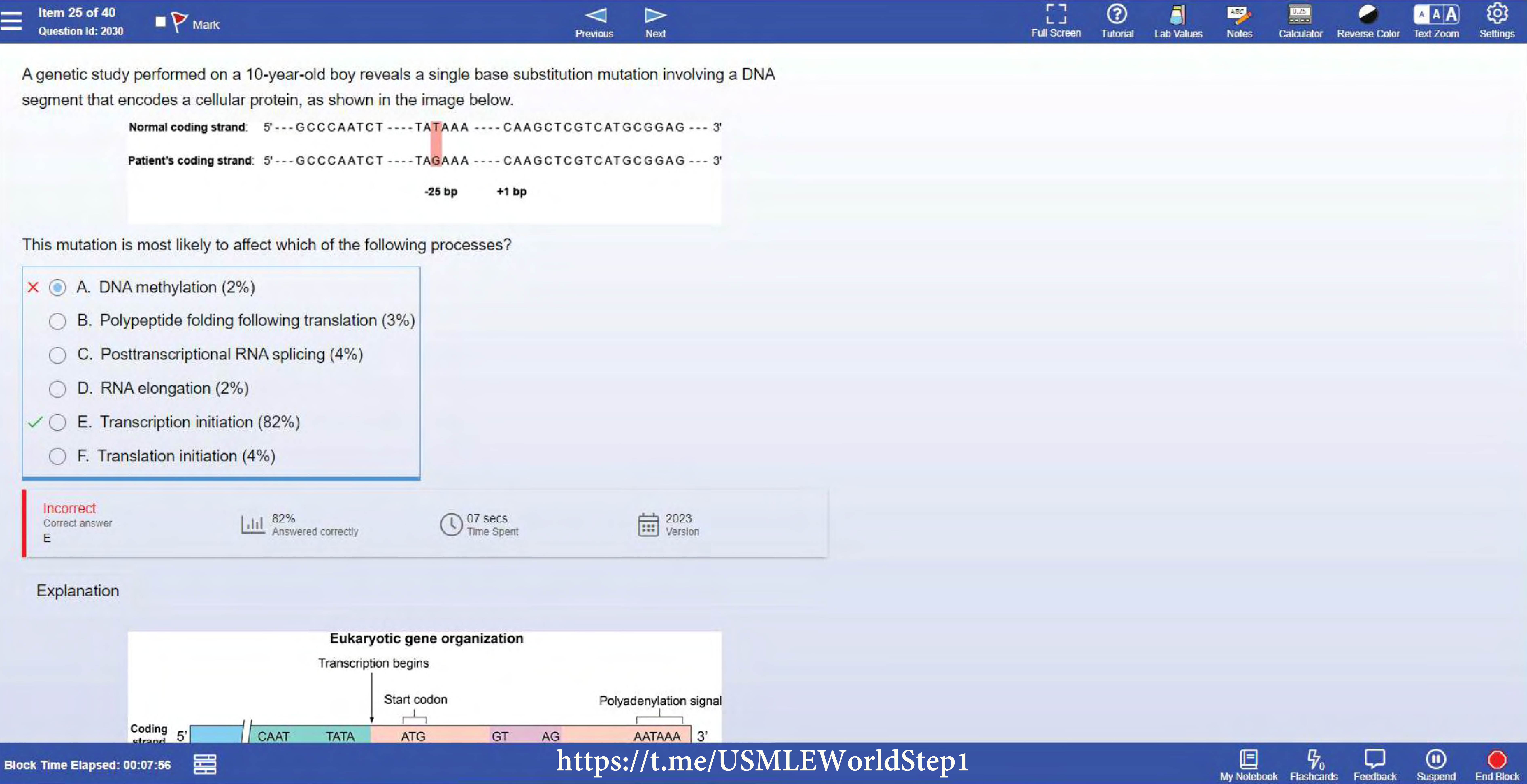
Item 25 of 40
Question Id: 2030
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A genetic study performed on a 10-year-old boy reveals a single base substitution mutation involving a DNA segment that encodes a cellular protein, as shown in the image below.

Normal coding strand: 5'---GCCCAATCT----TATAAA----CAAGCTCGTCATGCGGAG---3'

Patient's coding strand: 5'---GCCCAATCT----TAGAAA----CAAGCTCGTCATGCGGAG---3'

-25 bp **+1 bp**

This mutation is most likely to affect which of the following processes?

- ✗ ● A. DNA methylation (2%)
- ○ B. Polypeptide folding following translation (3%)
- ○ C. Posttranscriptional RNA splicing (4%)
- ○ D. RNA elongation (2%)
- ✓ ○ E. Transcription initiation (82%)
- ○ F. Translation initiation (4%)

Incorrect
Correct answer
E

82%
Answered correctly

07 secs
Time Spent

2023
Version

Explanation

Eukaryotic gene organization

Transcription begins
Start codon
Polyadenylation signal
Coding strand
5'
CAAT
TATA
ATG
GT
AG
AATAAA
3'

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Flashcards
Feedback
Suspend
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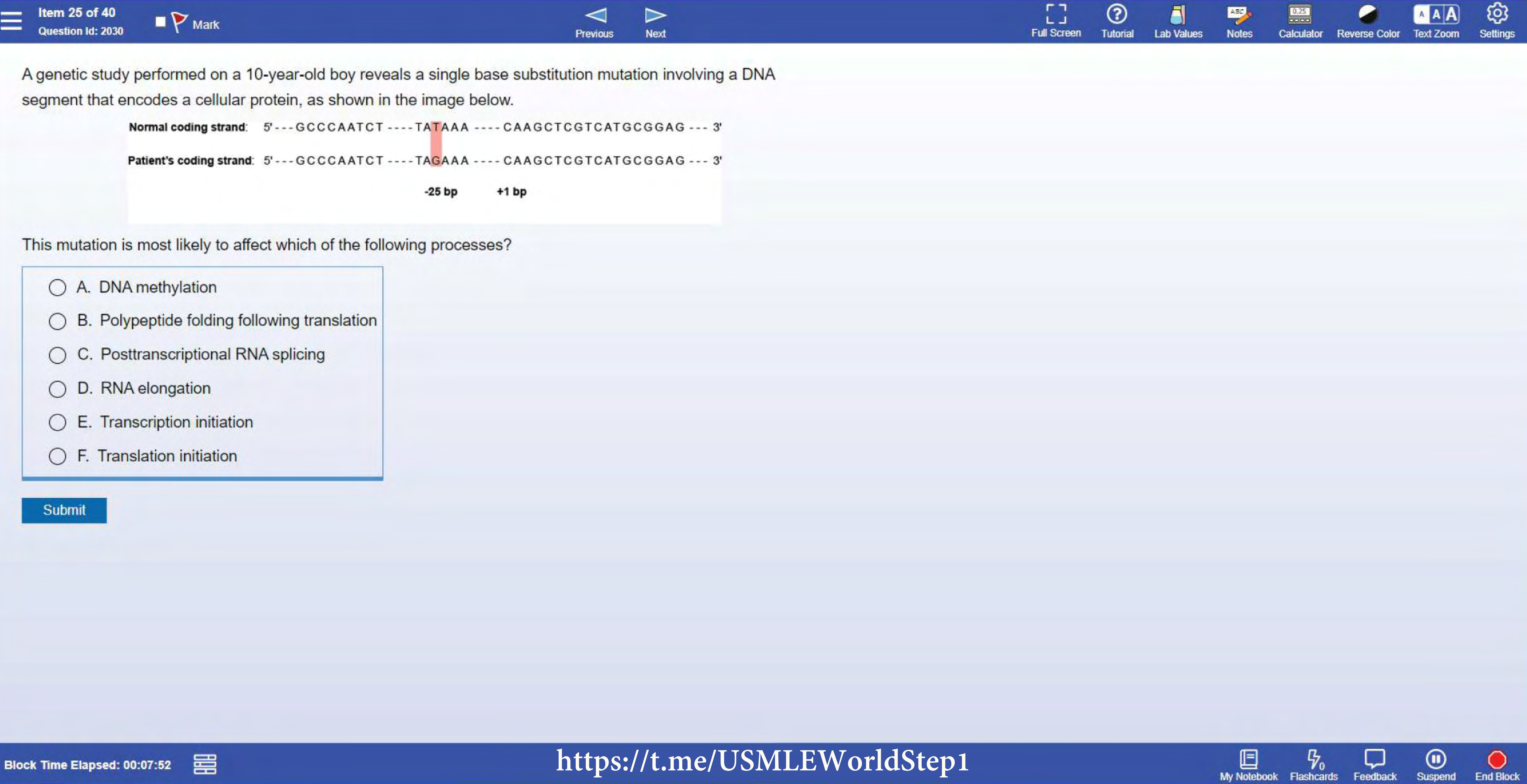

Item 25 of 40
Question Id: 2030
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Normal coding strand: 5'---GCCCAATCT----TATAAA----CAAGCTCGTCATGCGGAG---3'

Patient's coding strand: 5'---GCCCAATCT----TAGAAA----CAAGCTCGTCATGCGGAG---3'

-25 bp **+1 bp**

This mutation is most likely to affect which of the following processes?

○ A. DNA methylation
○ B. Polypeptide folding following translation
○ C. Posttranscriptional RNA splicing
○ D. RNA elongation
○ E. Transcription initiation
○ F. Translation initiation

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My Notebook
Flashcards
Feedback
Suspend
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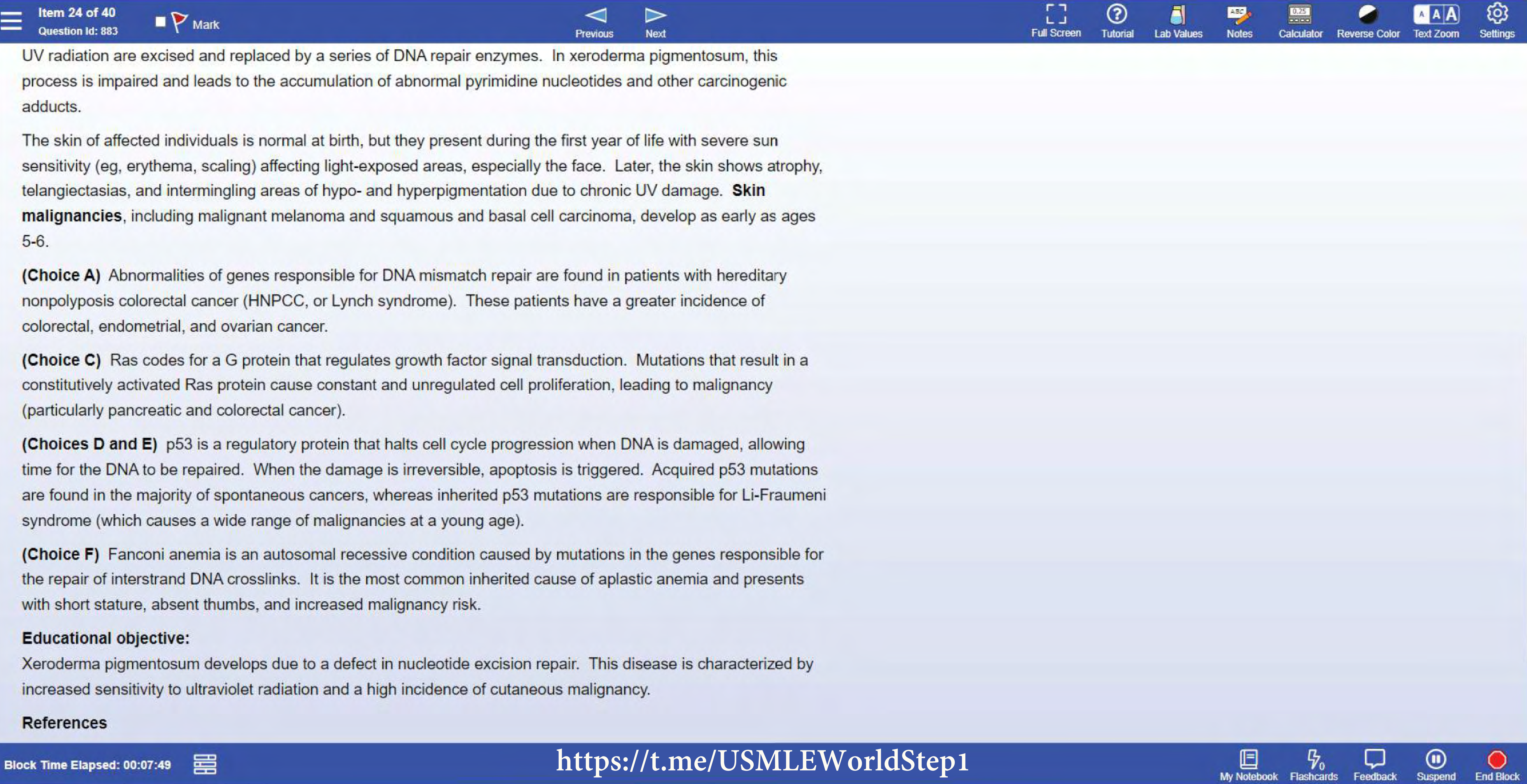


UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other carcinogenic adducts.

The skin of affected individuals is normal at birth, but they present during the first year of life with severe sun sensitivity (eg, erythema, scaling) affecting light-exposed areas, especially the face. Later, the skin shows atrophy, telangiectasias, and intermingling areas of hypo- and hyperpigmentation due to chronic UV damage. **Skin malignancies**, including malignant melanoma and squamous and basal cell carcinoma, develop as early as ages 5-6.

(Choice A) Abnormalities of genes responsible for DNA mismatch repair are found in patients with hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome). These patients have a greater incidence of colorectal, endometrial, and ovarian cancer.

(Choice C) Ras codes for a G protein that regulates growth factor signal transduction. Mutations that result in a constitutively activated Ras protein cause constant and unregulated cell proliferation, leading to malignancy (particularly pancreatic and colorectal cancer).

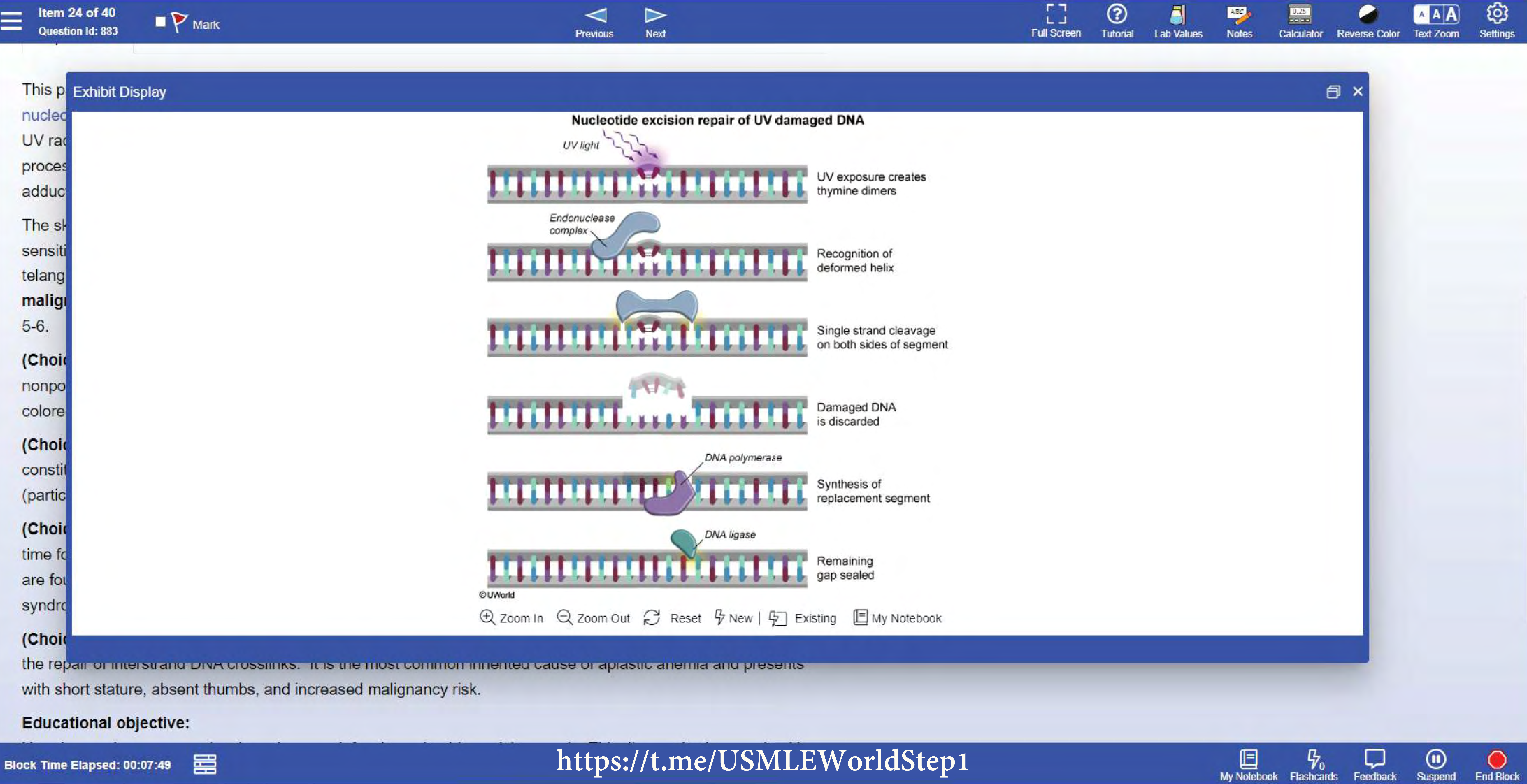
(Choices D and E) p53 is a regulatory protein that halts cell cycle progression when DNA is damaged, allowing time for the DNA to be repaired. When the damage is irreversible, apoptosis is triggered. Acquired p53 mutations are found in the majority of spontaneous cancers, whereas inherited p53 mutations are responsible for Li-Fraumeni syndrome (which causes a wide range of malignancies at a young age).

(Choice F) Fanconi anemia is an autosomal recessive condition caused by mutations in the genes responsible for the repair of interstrand DNA crosslinks. It is the most common inherited cause of aplastic anemia and presents with short stature, absent thumbs, and increased malignancy risk.

Educational objective:

Xeroderma pigmentosum develops due to a defect in nucleotide excision repair. This disease is characterized by increased sensitivity to ultraviolet radiation and a high incidence of cutaneous malignancy.

References



Item 24 of 40
Question Id: 883
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Nucleotide excision repair of UV damaged DNA

UV light
UV exposure creates thymine dimers
Endonuclease complex
Recognition of deformed helix
Single strand cleavage on both sides of segment
Damaged DNA is discarded
DNA polymerase
Synthesis of replacement segment
DNA ligase
Remaining gap sealed
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Zoom Out
Reset
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the repair of interstrand DNA crosslinks. It is the most common inherited cause of aplastic anemia and presents with short stature, absent thumbs, and increased malignancy risk.

Educational objective:

Block Time Elapsed: 00:07:49
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 24 of 40
Question Id: 883
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Xeroderma pigmentosum develops due to a defect in nucleotide excision repair. This disease is characterized by increased sensitivity to ultraviolet radiation and a high incidence of cutaneous malignancy.

References

- Xeroderma pigmentosum
- Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect.

Genetics	Genetics (General Principles)	Xeroderma pigmentosum
Subject	System	Topic

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My Notebook
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Feedback
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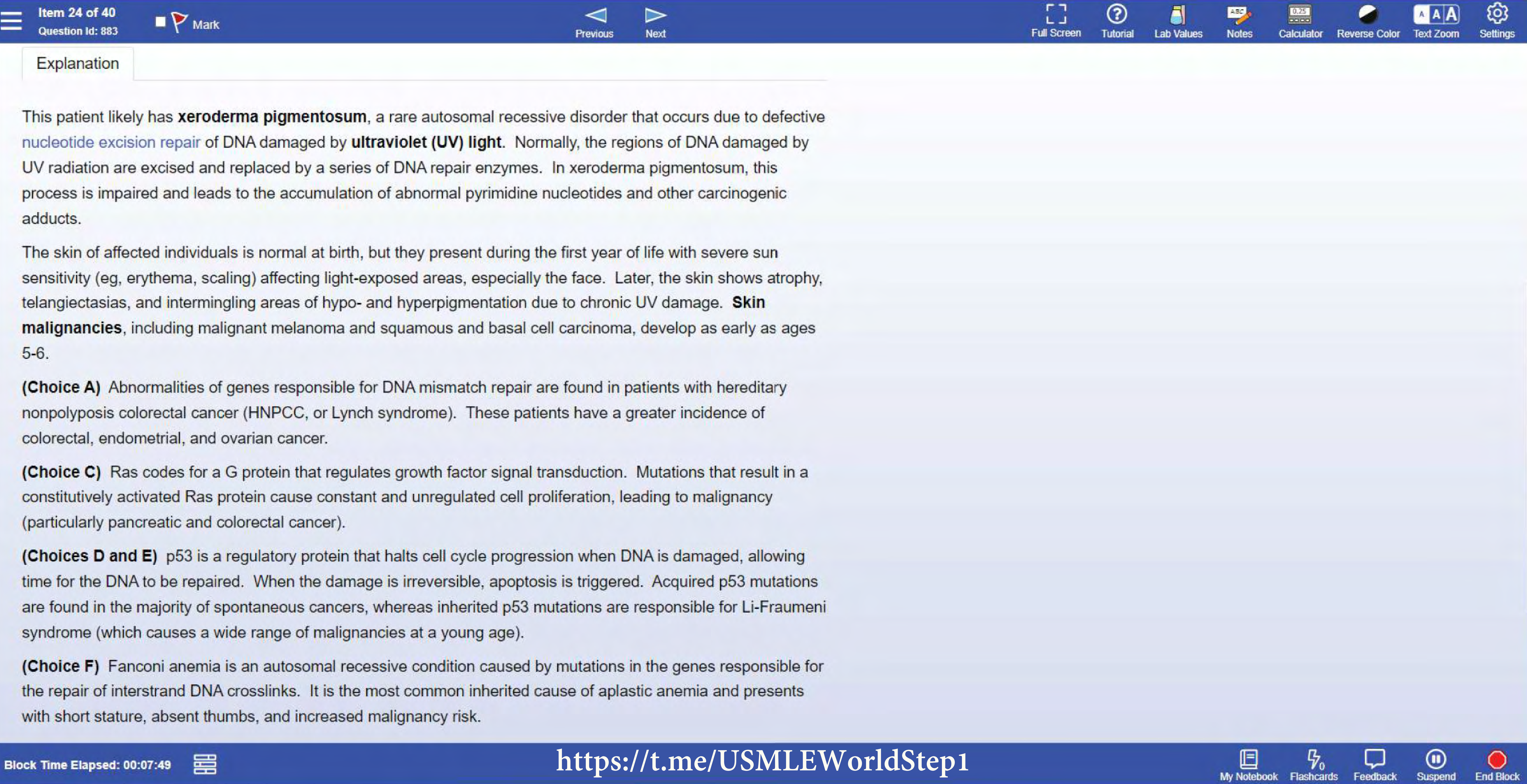

This patient likely has **xeroderma pigmentosum**, a rare autosomal recessive disorder that occurs due to defective nucleotide excision repair of DNA damaged by **ultraviolet (UV) light**. Normally, the regions of DNA damaged by UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other carcinogenic adducts.

The skin of affected individuals is normal at birth, but they present during the first year of life with severe sun sensitivity (eg, erythema, scaling) affecting light-exposed areas, especially the face. Later, the skin shows atrophy, telangiectasias, and intermingling areas of hypo- and hyperpigmentation due to chronic UV damage. **Skin malignancies**, including malignant melanoma and squamous and basal cell carcinoma, develop as early as ages 5-6.

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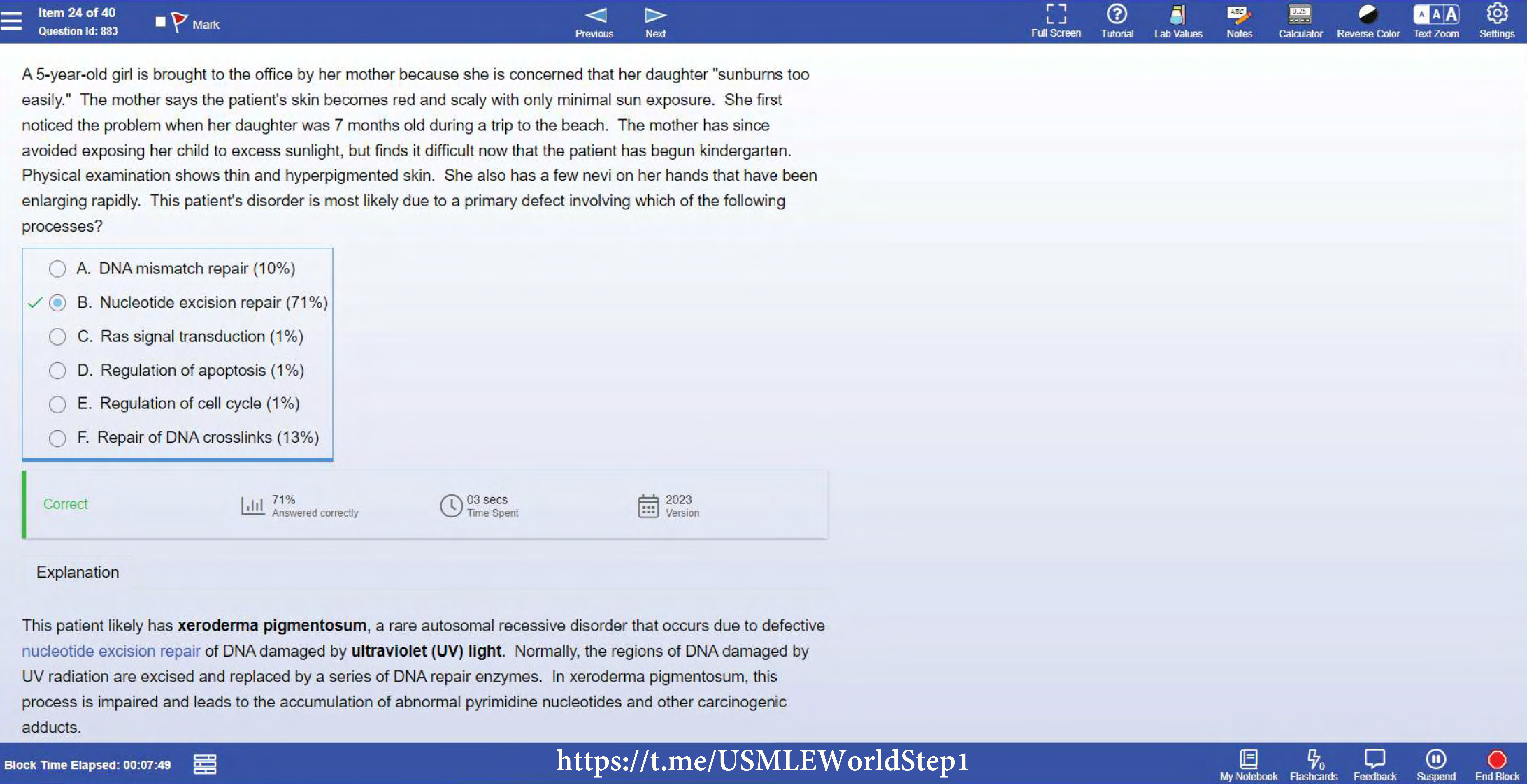
Item 24 of 40
Question Id: 883
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 5-year-old girl is brought to the office by her mother because she is concerned that her daughter "sunburns too easily." The mother says the patient's skin becomes red and scaly with only minimal sun exposure. She first noticed the problem when her daughter was 7 months old during a trip to the beach. The mother has since avoided exposing her child to excess sunlight, but finds it difficult now that the patient has begun kindergarten. Physical examination shows thin and hyperpigmented skin. She also has a few nevi on her hands that have been enlarging rapidly. This patient's disorder is most likely due to a primary defect involving which of the following processes?

- ○ A. DNA mismatch repair (10%)
- ✓ ● B. Nucleotide excision repair (71%)
- ○ C. Ras signal transduction (1%)
- ○ D. Regulation of apoptosis (1%)
- ○ E. Regulation of cell cycle (1%)
- ○ F. Repair of DNA crosslinks (13%)

Correct | 71% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

This patient likely has **xeroderma pigmentosum**, a rare autosomal recessive disorder that occurs due to defective nucleotide excision repair of DNA damaged by **ultraviolet (UV) light**. Normally, the regions of DNA damaged by UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other carcinogenic adducts.

Block Time Elapsed: 00:07:49

My Notebook
Flashcards
Feedback
Suspend
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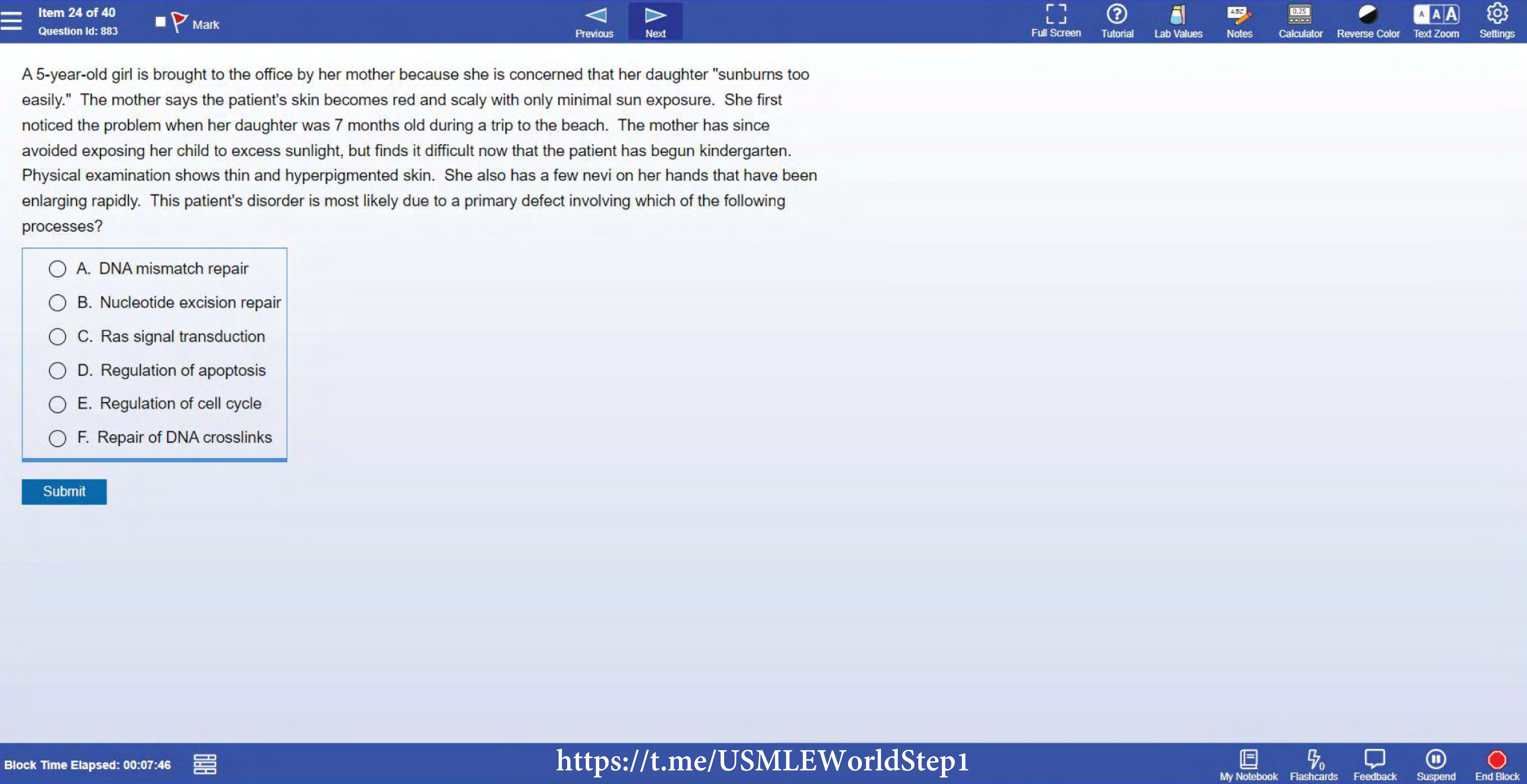
Item 24 of 40
Question Id: 883
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:07:46
My Notebook
Flashcards
Feedback
Suspend
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A 5-year-old girl is brought to the office by her mother because she is concerned that her daughter "sunburns too easily." The mother says the patient's skin becomes red and scaly with only minimal sun exposure. She first noticed the problem when her daughter was 7 months old during a trip to the beach. The mother has since avoided exposing her child to excess sunlight, but finds it difficult now that the patient has begun kindergarten. Physical examination shows thin and hyperpigmented skin. She also has a few nevi on her hands that have been enlarging rapidly. This patient's disorder is most likely due to a primary defect involving which of the following processes?

○ A. DNA mismatch repair
○ B. Nucleotide excision repair
○ C. Ras signal transduction
○ D. Regulation of apoptosis
○ E. Regulation of cell cycle
○ F. Repair of DNA crosslinks

Item 23 of 40
Question Id: 2034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

2. Restriction endonuclease digestion of the DNA sample into fragments
3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster
4. DNA probe (a single-stranded segment of labeled DNA complementary to the gene of interest) to identify the target gene

Once the gene of interest is identified by the DNA probe, various family members' Southern blots can be compared. Because **both** the patient and his father are affected, the common DNA segment between them (**8 kb segment**) most likely represents the mutated gene. The patient's **son** also has the 8 kb segment, meaning that he is probably affected as well.

(Choice A) Familial hypercholesterolemia is an autosomal dominant disorder. X-linked recessive mutations are transmitted from unaffected carrier mothers to their sons. Father-to-son transmission does not occur.

(Choices B and D) The patient (affected by the disease) does not possess the 10 kb segment, so this segment does not correspond to the mutated gene. The patient's brother inherited the 10 kb segment from his father (not the 8kb mutated segment), so he would not be affected.

(Choice C) The patient and his brother, but not their father, have a 12 kb segment on Southern blot analysis. Therefore, this segment was likely inherited from the mother and does not carry the mutation.

Educational objective:
Southern blotting is a technique used to identify DNA mutations. It involves restriction endonuclease digestion of sample DNA, gel electrophoresis, and gene identification with a labeled DNA probe.

References

- Genetic defects causing familial hypercholesterolaemia: identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic.

Biochemistry	Genetics (General Principles)	Genetic testing
Subject	System	Topic

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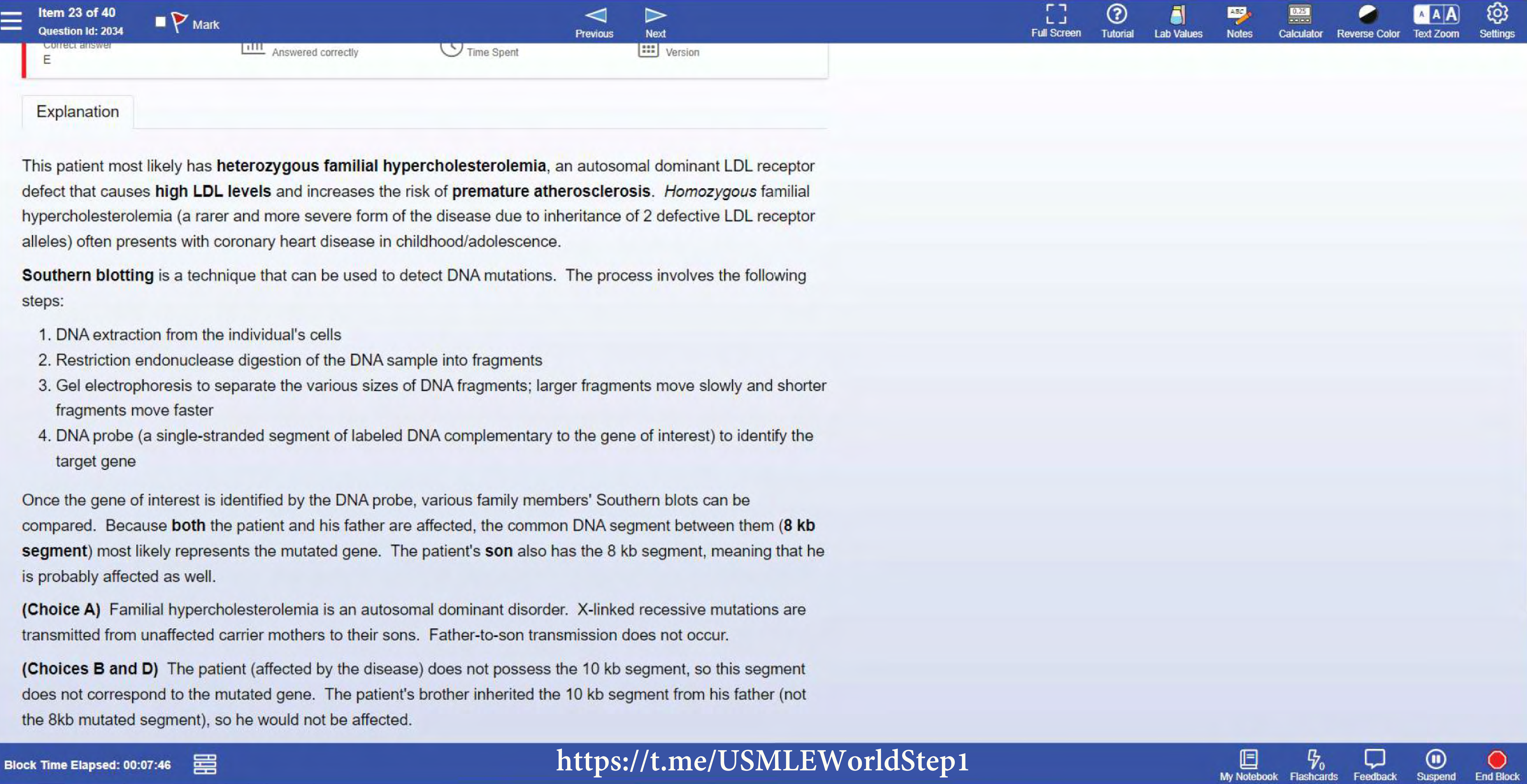

Item 23 of 40
Question Id: 2034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Correct answer
E
Answered correctly
Time Spent
Version
Explanation
Block Time Elapsed: 00:07:46
My Notebook
Flashcards
Feedback
Suspend
End Block

This patient most likely has **heterozygous familial hypercholesterolemia**, an autosomal dominant LDL receptor defect that causes **high LDL levels** and increases the risk of **premature atherosclerosis**. *Homozygous* familial hypercholesterolemia (a rarer and more severe form of the disease due to inheritance of 2 defective LDL receptor alleles) often presents with coronary heart disease in childhood/adolescence.

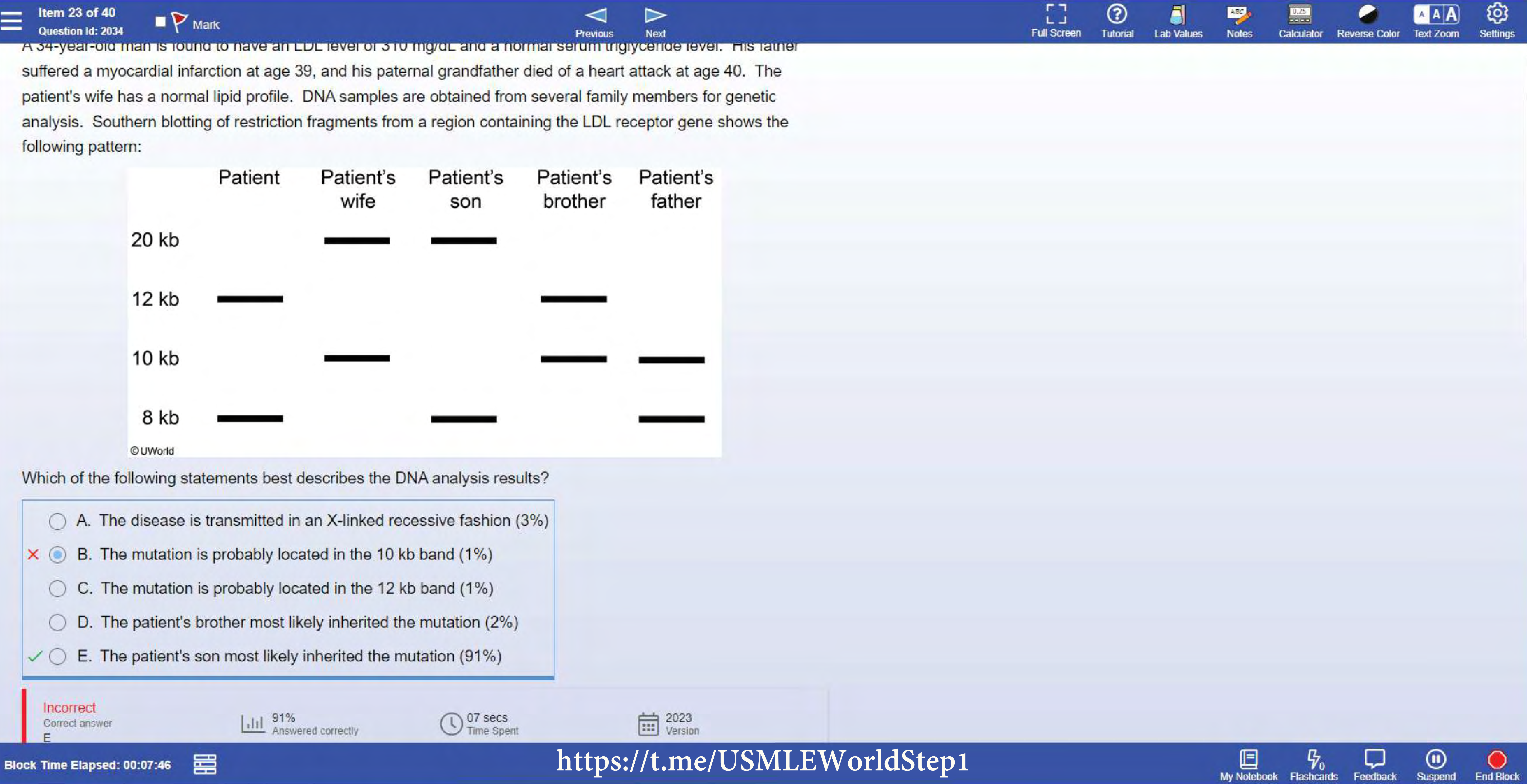
Southern blotting is a technique that can be used to detect DNA mutations. The process involves the following steps:

1. DNA extraction from the individual's cells
2. Restriction endonuclease digestion of the DNA sample into fragments
3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster
4. DNA probe (a single-stranded segment of labeled DNA complementary to the gene of interest) to identify the target gene

Once the gene of interest is identified by the DNA probe, various family members' Southern blots can be compared. Because **both** the patient and his father are affected, the common DNA segment between them (**8 kb segment**) most likely represents the mutated gene. The patient's **son** also has the 8 kb segment, meaning that he is probably affected as well.

(Choice A) Familial hypercholesterolemia is an autosomal dominant disorder. X-linked recessive mutations are transmitted from unaffected carrier mothers to their sons. Father-to-son transmission does not occur.

(Choices B and D) The patient (affected by the disease) does not possess the 10 kb segment, so this segment does not correspond to the mutated gene. The patient's brother inherited the 10 kb segment from his father (not the 8kb mutated segment), so he would not be affected.


Item 23 of 40
Question Id: 2034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 34-year-old man is found to have an LDL level of 310 mg/dL and a normal serum triglyceride level. His father suffered a myocardial infarction at age 39, and his paternal grandfather died of a heart attack at age 40. The patient's wife has a normal lipid profile. DNA samples are obtained from several family members for genetic analysis. Southern blotting of restriction fragments from a region containing the LDL receptor gene shows the following pattern:

	Patient	Patient's wife	Patient's son	Patient's brother	Patient's father
20 kb		▬	▬		
12 kb	▬			▬	
10 kb		▬		▬	▬
8 kb	▬		▬		▬

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Which of the following statements best describes the DNA analysis results?

○ A. The disease is transmitted in an X-linked recessive fashion (3%)

✕ ● B. The mutation is probably located in the 10 kb band (1%)

○ C. The mutation is probably located in the 12 kb band (1%)

○ D. The patient's brother most likely inherited the mutation (2%)

✓ ○ E. The patient's son most likely inherited the mutation (91%)

Incorrect
Correct answer
E

91%
Answered correctly

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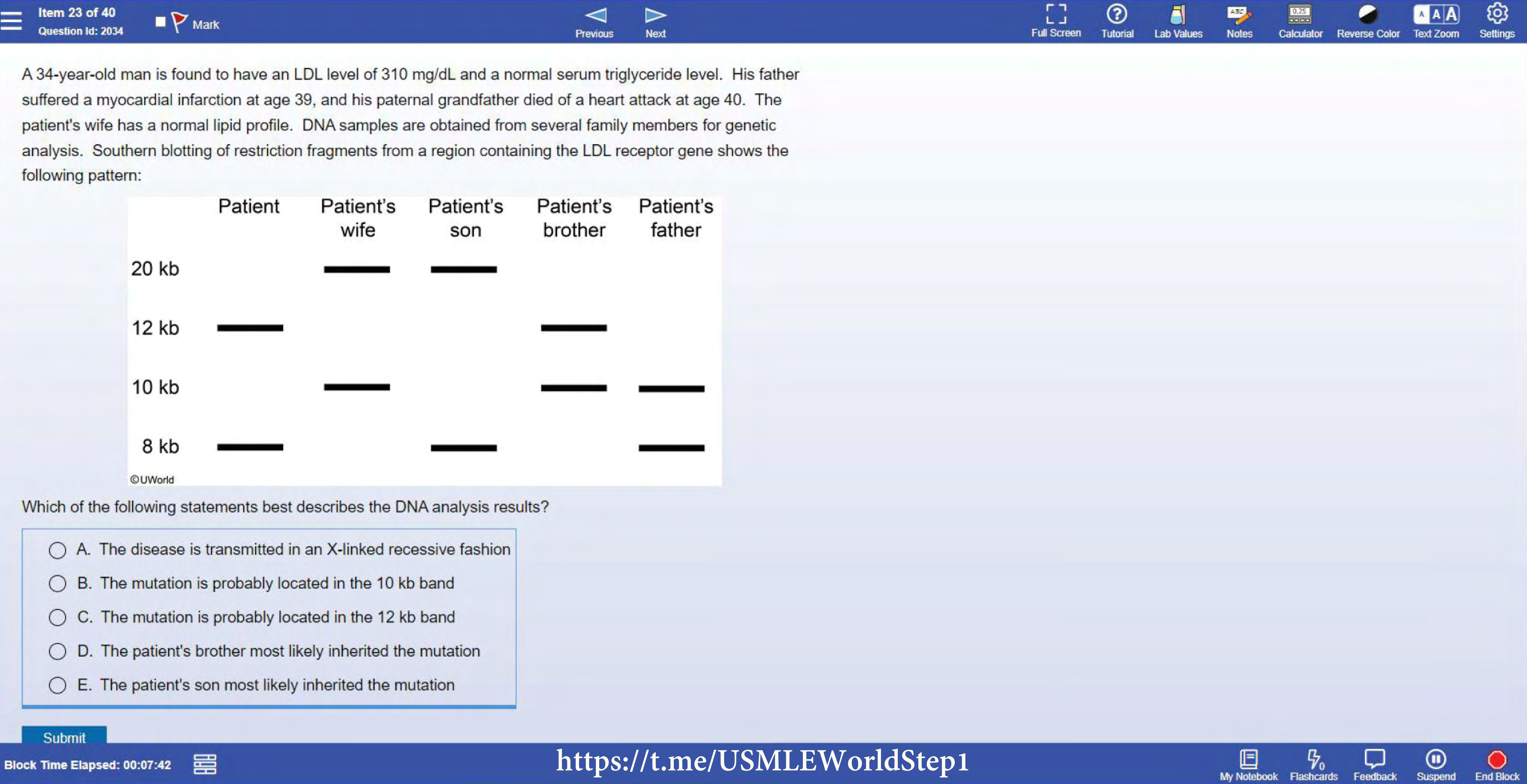
Time Spent

2023
Version

Block Time Elapsed: 00:07:46
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 23 of 40
Question Id: 2034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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	Patient	Patient's wife	Patient's son	Patient's brother	Patient's father
20 kb		▬	▬		
12 kb	▬			▬	
10 kb		▬		▬	▬
8 kb	▬		▬		▬

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Which of the following statements best describes the DNA analysis results?

○ A. The disease is transmitted in an X-linked recessive fashion
○ B. The mutation is probably located in the 10 kb band
○ C. The mutation is probably located in the 12 kb band
○ D. The patient's brother most likely inherited the mutation
○ E. The patient's son most likely inherited the mutation

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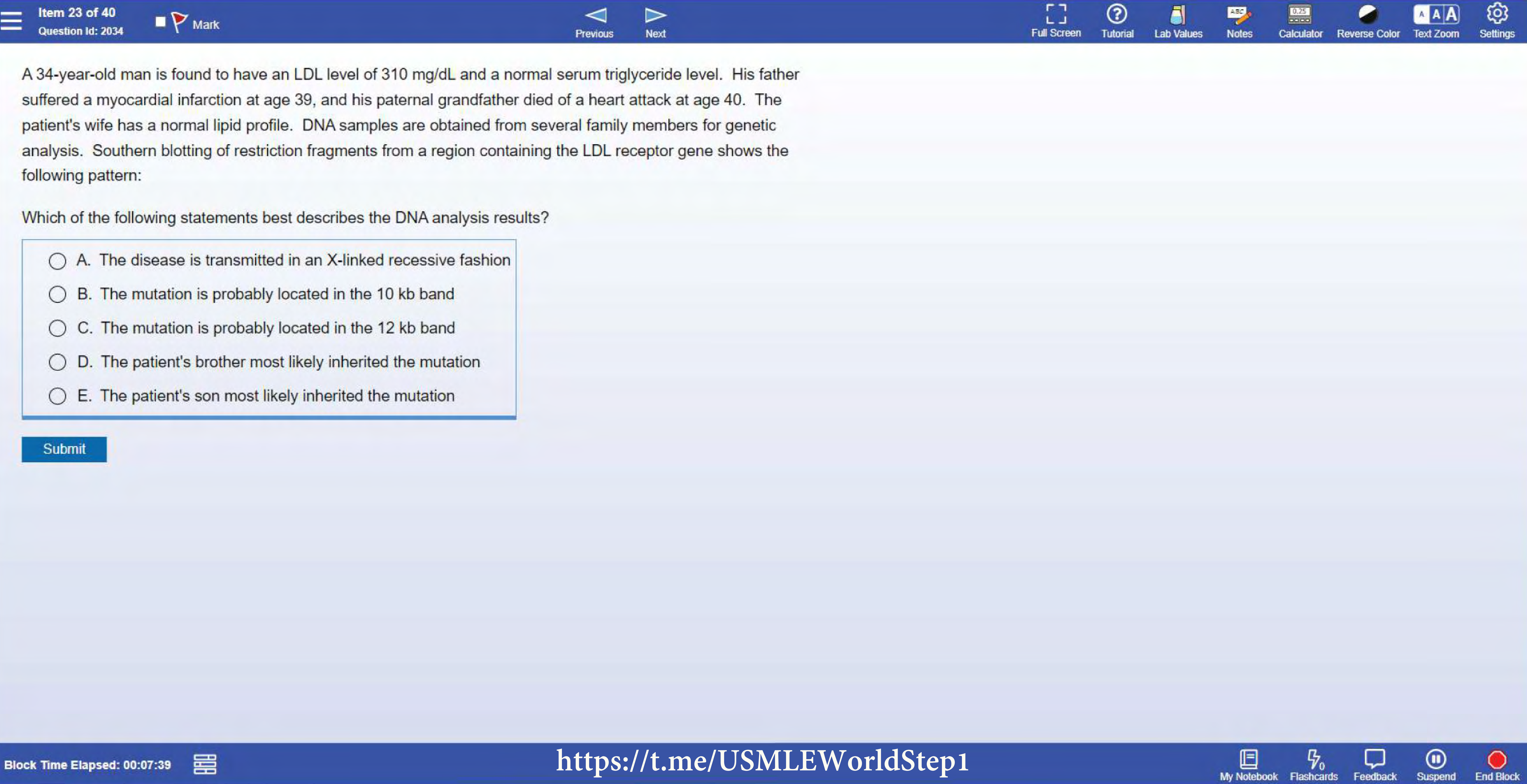
Flashcards
Feedback
Suspend
End Block


Item 23 of 40
Question Id: 2034
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 34-year-old man is found to have an LDL level of 310 mg/dL and a normal serum triglyceride level. His father suffered a myocardial infarction at age 39, and his paternal grandfather died of a heart attack at age 40. The patient's wife has a normal lipid profile. DNA samples are obtained from several family members for genetic analysis. Southern blotting of restriction fragments from a region containing the LDL receptor gene shows the following pattern:

Which of the following statements best describes the DNA analysis results?

○ A. The disease is transmitted in an X-linked recessive fashion
○ B. The mutation is probably located in the 10 kb band
○ C. The mutation is probably located in the 12 kb band
○ D. The patient's brother most likely inherited the mutation
○ E. The patient's son most likely inherited the mutation

Submit
Block Time Elapsed: 00:07:39
My Notebook
Flashcards
Feedback
Suspend
End Block

chain.

Transfer RNA molecules (**tRNA**) transport amino acids to the ribosome and ensure placement of the proper amino acid. One end of the molecule serves as the amino acid binding site; the opposite end contains a specific nucleic acid sequence known as the **anticodon** that is **complementary** to one or more **mRNA codons** (due to base wobbling). The type of amino acid that is bound to each tRNA molecule is determined by its anticodon sequence; this ensures that the proper amino acid is added at each mRNA codon during protein synthesis.

Translation of the mRNA template proceeds in the 5' to 3' direction. The mRNA of the dysfunctional protein in the question stem contains an extra stop codon (UAA) before the normal stop codon (UAG) at the end of the template. During protein translation, the **first stop codon** encountered will **bind a release factor**, halting protein synthesis. Therefore, the codon just prior to the first stop codon will be the last codon to add an amino acid. In this case, (**5'-UUG-3'**) is the last codon to add an amino acid to the truncated protein, and this amino acid will be carried by the **5'-CAA-3'** anticodon (codon-anticodon binding occurs in opposite directions [ie, **5' to 3' binds 3' to 5'**]).

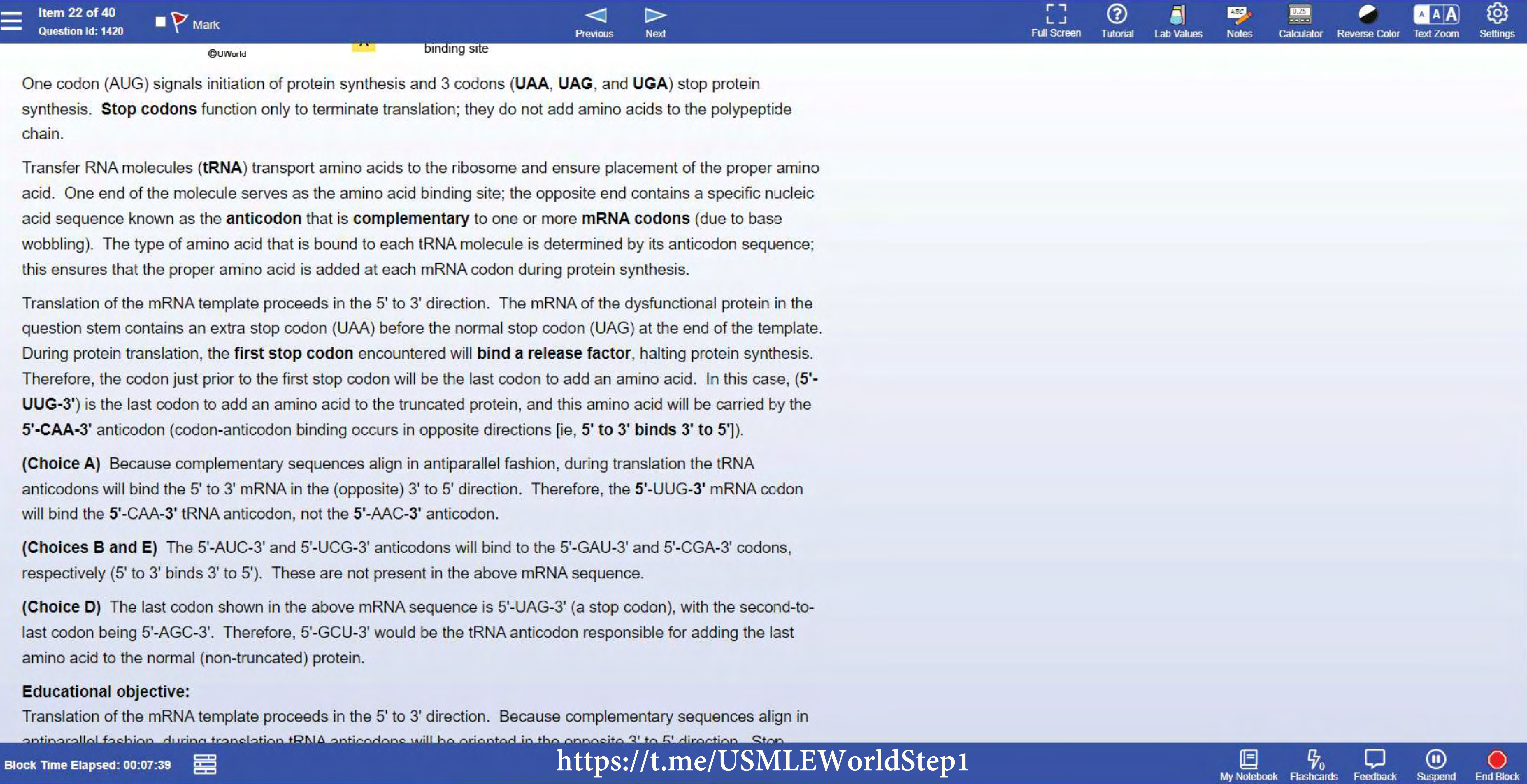
(Choice A) Because complementary sequences align in antiparallel fashion, during translation the tRNA anticodons will bind the 5' to 3' mRNA in the (opposite) 3' to 5' direction. Therefore, the **5'**-UUG-**3'** mRNA codon will bind the **5'**-CAA-**3'** tRNA anticodon, not the **5'**-AAC-**3'** anticodon.

(Choices B and E) The 5'-AUC-3' and 5'-UCG-3' anticodons will bind to the 5'-GAU-3' and 5'-CGA-3' codons, respectively (5' to 3' binds 3' to 5'). These are not present in the above mRNA sequence.

(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'. Therefore, 5'-GCU-3' would be the tRNA anticodon responsible for adding the last amino acid to the normal (non-truncated) protein.

Educational objective:

Translation of the mRNA template proceeds in the 5' to 3' direction. Because complementary sequences align in antiparallel fashion, during translation tRNA anticodons will be oriented in the opposite 3' to 5' direction. Stop codons (UAA, UAG, and UGA) halt protein synthesis by binding a release factor; they do not add amino acids to the polypeptide chain.



One codon (AUG) signals initiation of protein synthesis and 3 codons (**UAA**, **UAG**, and **UGA**) stop protein synthesis. **Stop codons** function only to terminate translation; they do not add amino acids to the polypeptide chain.

Transfer RNA molecules (**tRNA**) transport amino acids to the ribosome and ensure placement of the proper amino acid. One end of the molecule serves as the amino acid binding site; the opposite end contains a specific nucleic acid sequence known as the **anticodon** that is **complementary** to one or more **mRNA codons** (due to base wobbling). The type of amino acid that is bound to each tRNA molecule is determined by its anticodon sequence; this ensures that the proper amino acid is added at each mRNA codon during protein synthesis.

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(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'. Therefore, 5'-GCU-3' would be the tRNA anticodon responsible for adding the last amino acid to the normal (non-truncated) protein.

Educational objective:

Translation of the mRNA template proceeds in the 5' to 3' direction. Because complementary sequences align in antiparallel fashion, during translation tRNA anticodons will be oriented in the opposite 3' to 5' direction. Stop

✓ ○ C. 5'-CAA-3' (32%)

○

○

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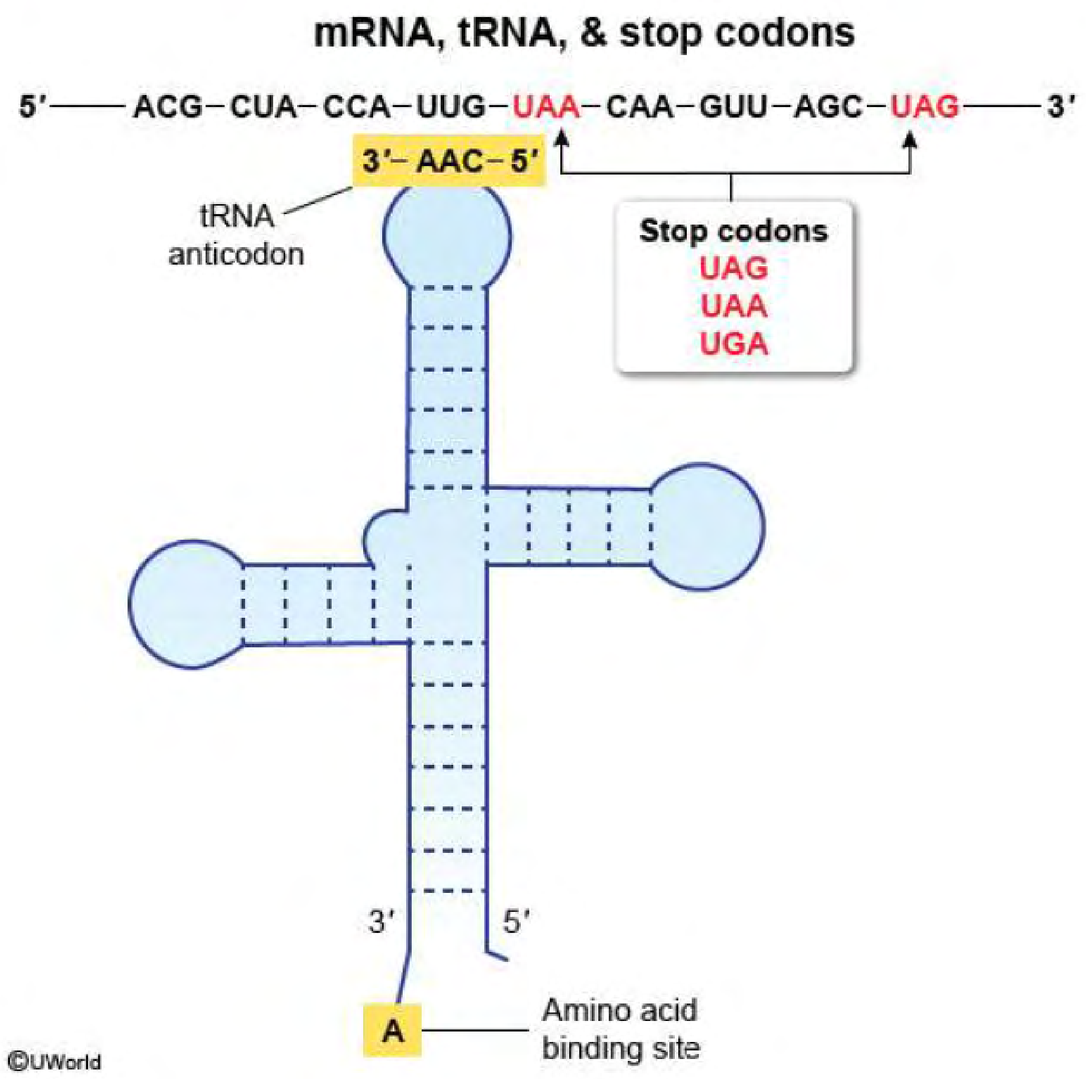
mRNA, tRNA, & stop codons

5′—ACG–CUA–CCA–UUG–UAA–CAA–GUU–AGC–UAG—3′
3′–AAC–5′
tRNA anticodon
Stop codons
UAG
UAA
UGA
3′
5′
A
Amino acid binding site
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Zoom Out
Reset
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A
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binding site
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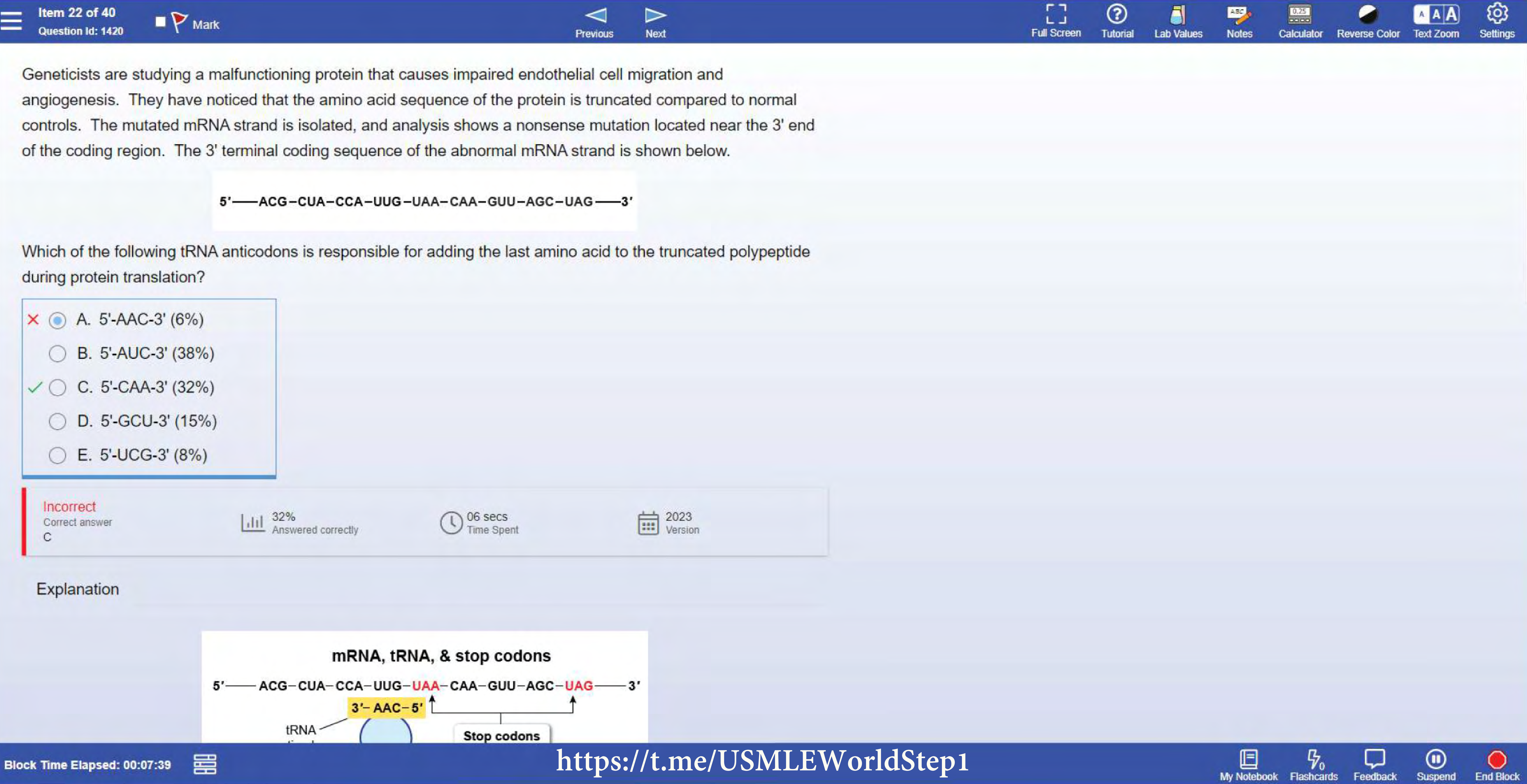
Item 22 of 40
Question Id: 1420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Geneticists are studying a malfunctioning protein that causes impaired endothelial cell migration and angiogenesis. They have noticed that the amino acid sequence of the protein is truncated compared to normal controls. The mutated mRNA strand is isolated, and analysis shows a nonsense mutation located near the 3' end of the coding region. The 3' terminal coding sequence of the abnormal mRNA strand is shown below.

5'——ACG–CUA–CCA–UUG–UAA–CAA–GUU–AGC–UAG——3'

Which of the following tRNA anticodons is responsible for adding the last amino acid to the truncated polypeptide during protein translation?

✗ ● A. 5'-AAC-3' (6%)
○ B. 5'-AUC-3' (38%)
✓ ○ C. 5'-CAA-3' (32%)
○ D. 5'-GCU-3' (15%)
○ E. 5'-UCG-3' (8%)

Incorrect
Correct answer
C

32%
Answered correctly

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Time Spent

2023
Version

Explanation

mRNA, tRNA, & stop codons

5'——ACG–CUA–CCA–UUG–UAA–CAA–GUU–AGC–UAG——3'
3'–AAC–5'
tRNA
Stop codons

Block Time Elapsed: 00:07:39
My Notebook
Flashcards
Feedback
Suspend
End Block

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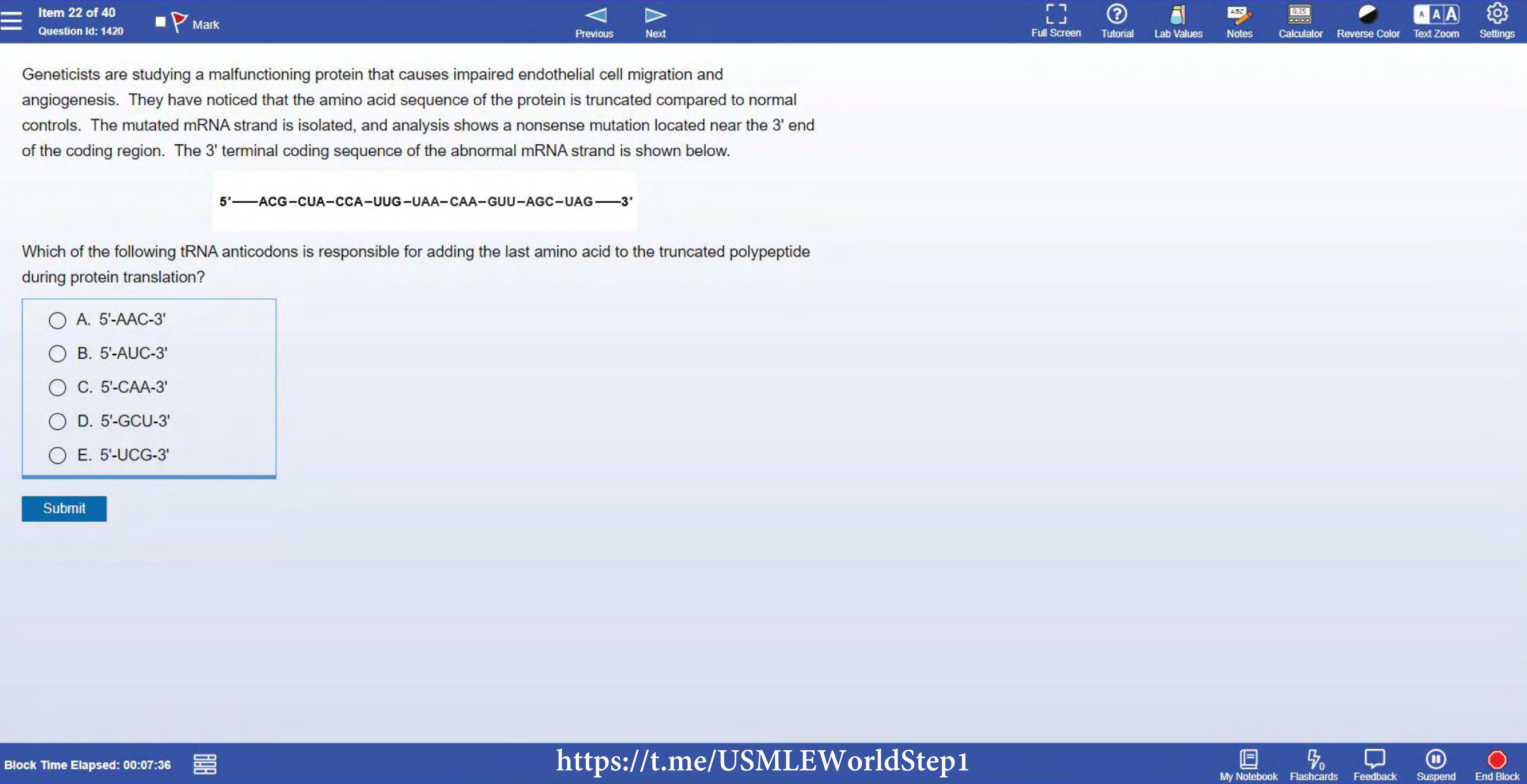
Item 22 of 40
Question Id: 1420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

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- ○ B. 5'-AUC-3'
- ○ C. 5'-CAA-3'
- ○ D. 5'-GCU-3'
- ○ E. 5'-UCG-3'

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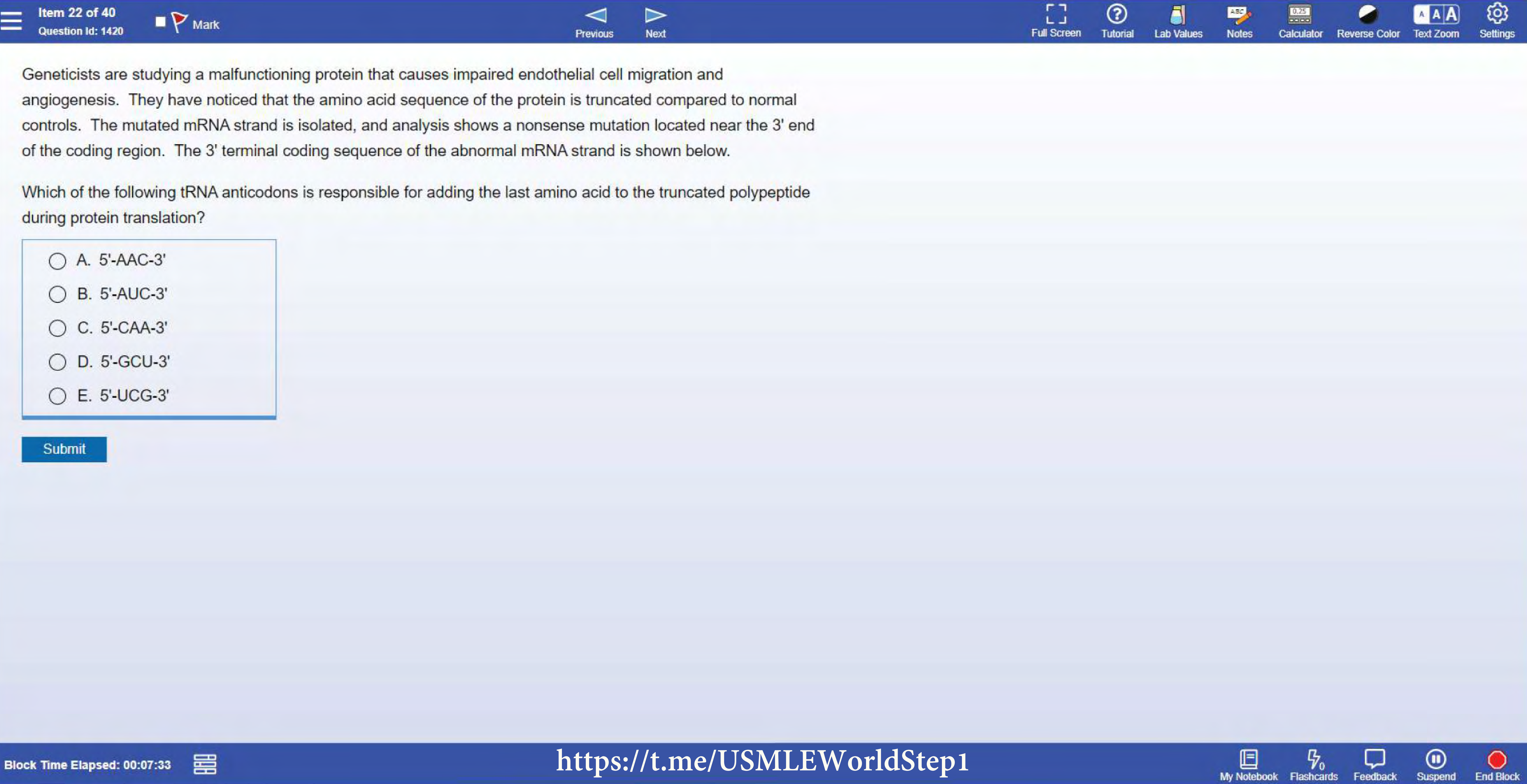
Block Time Elapsed: 00:07:36


Item 22 of 40
Question Id: 1420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:07:33
My Notebook
Flashcards
Feedback
Suspend
End Block

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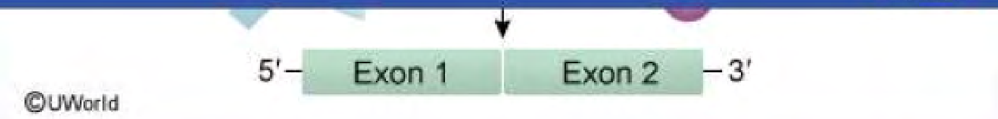
- ○ C. 5'-CAA-3'
- ○ D. 5'-GCU-3'
- ○ E. 5'-UCG-3'



Following transcription, pre-mRNA is the initial transcript that contains both intron and exon sequences. Before leaving the nucleus, pre-mRNA must be processed to mature mRNA by 3 post-transcriptional modifications: 5' methylguanosine capping, addition of a 3' polyadenine (Poly A) tail, and splicing.

Splicing is performed by **spliceosomes**, which are complexes of small nuclear ribonucleoproteins (snRNPs) and other proteins that assemble on pre-mRNA. Spliceosomes **remove introns** containing **GU** at the **5' splice site** and **AG** at the **3' splice site**. Initially, the 5' end of intron 1 (splice donor site) is cleaved and joined to the branch point. The freed 3'-OH of exon 1 then forms a phosphodiester bond with the 5'-phosphate at the splice acceptor site, joining exons 1 and 2. Mutations at splice sites may result in inappropriate removal of exons and retention of introns. This often leads to the formation of proteins with impaired structure and function as described in the case above.

(Choice A) Polyadenylation of the 3' end of mRNA is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA and helps it exit the nucleus.

(Choices B and D) In eukaryotes, translation is initiated when the small ribosomal subunit attaches to the 5' cap of mRNA and then scans for the AUG start codon within the Kozak consensus sequence. The 5' cap also protects against exonucleases and helps stabilize mRNA in the cytosol.

(Choice E) Termination of polypeptide synthesis occurs at the 3 stop codons (UAA, UAG, UGA) in mRNA. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an extremely long, nonfunctional polypeptide.

Educational objective:
Splicing is performed by spliceosomes, which remove introns containing GU at the 5' splice site and AG at the 3' splice site. Splice site mutations may result in inappropriate removal of exons and retention of introns, leading to the formation of dysfunctional proteins.

References

Familial dysautonomia is caused by mutations of the IKAP gene.

Item 21 of 40
Question Id: 2038

■ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

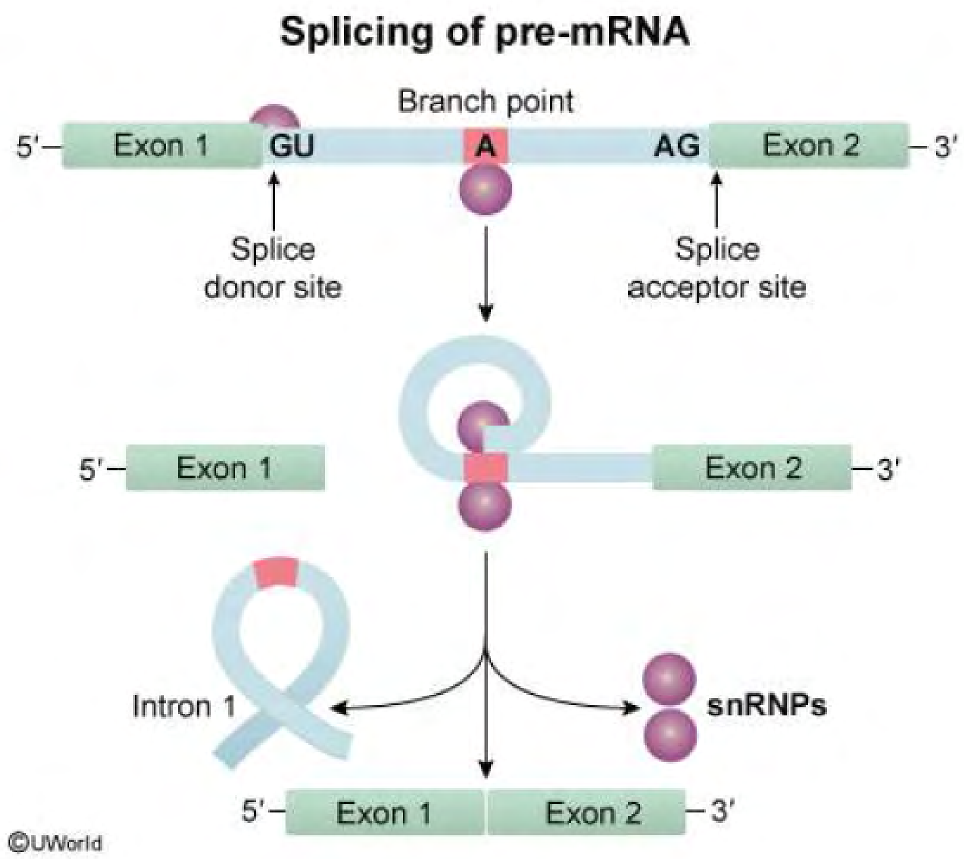
Correct answer
C

Answered correctly

Time Spent

Version

Exhibit Display



Splicing of pre-mRNA
Branch point
5′
Exon 1
GU
A
AG
Exon 2
3′
Splice donor site
Splice acceptor site
5′
Exon 1
Exon 2
3′
Intron 1
snRNPs
5′
Exon 1
Exon 2
3′
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Splicir
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and A
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site, joining exons 1 and 2. Mutations at splice sites may result in inappropriate removal of exons and retention of

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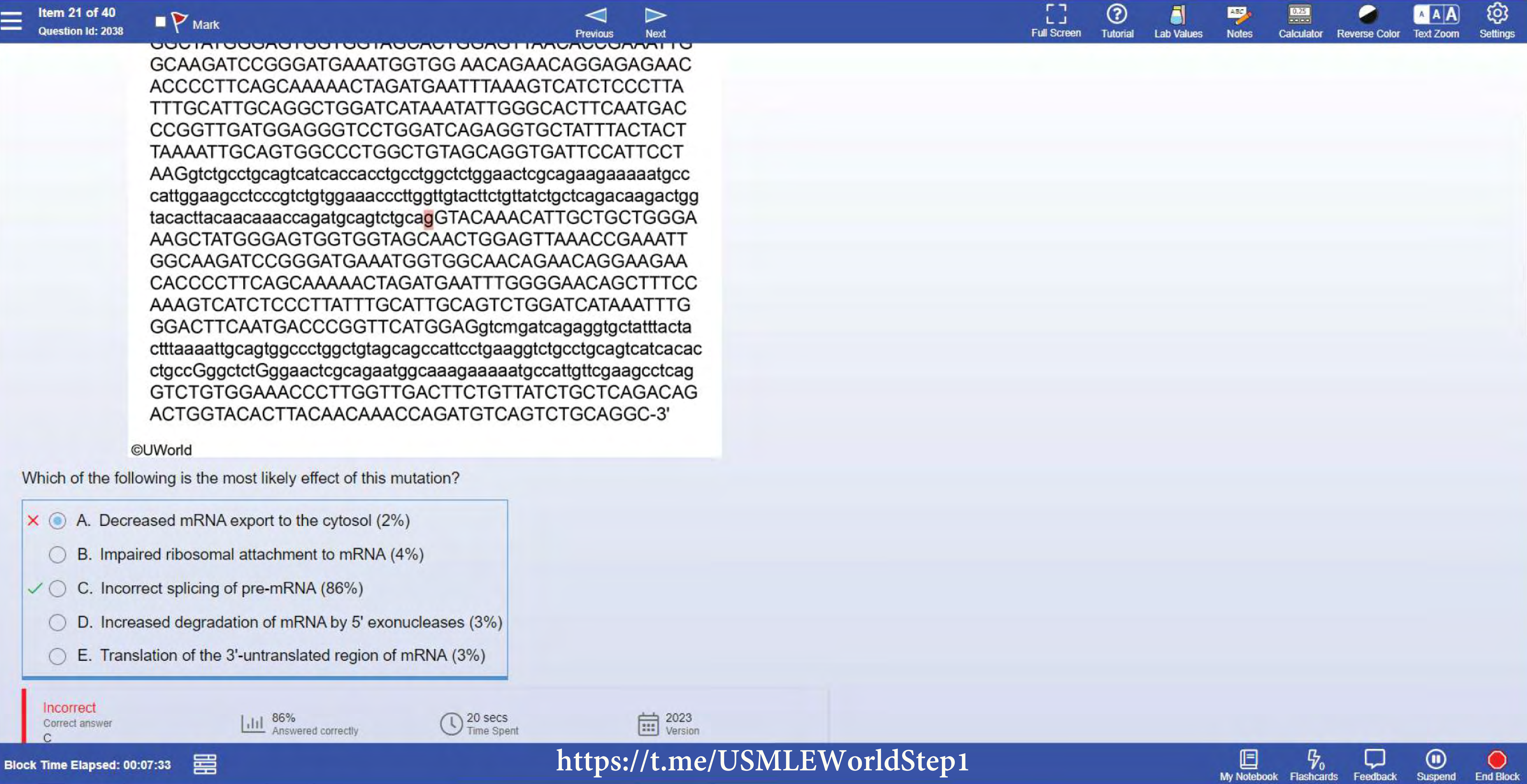

Item 21 of 40
Question Id: 2038
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

```
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ACCCCTTCAGCAAAAACTAGATGAATTTAAAGTCATCTCCCTTA
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CCGGTTGATGGAGGGTCCTGGATCAGAGGTGCTATTTACTACT
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ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'
```

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Which of the following is the most likely effect of this mutation?

- ✗ ● A. Decreased mRNA export to the cytosol (2%)
- ○ B. Impaired ribosomal attachment to mRNA (4%)
- ✓ ○ C. Incorrect splicing of pre-mRNA (86%)
- ○ D. Increased degradation of mRNA by 5' exonucleases (3%)
- ○ E. Translation of the 3'-untranslated region of mRNA (3%)

Incorrect
Correct answer
C

86%
Answered correctly

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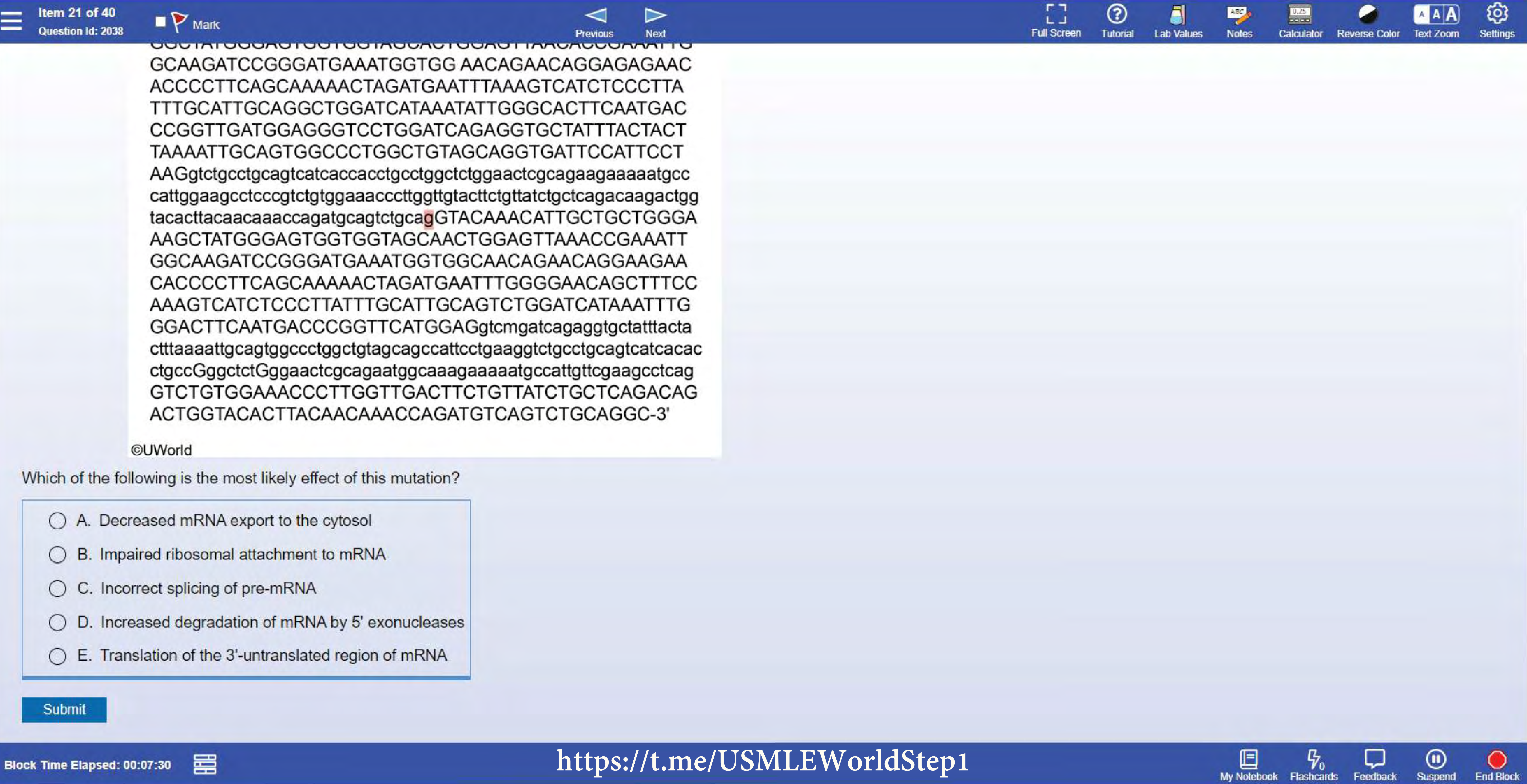
2023
Version

Block Time Elapsed: 00:07:33

My Notebook
Flashcards
Feedback
Suspend
End Block


Item 21 of 40
Question Id: 2038
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:07:30
My Notebook
Flashcards
Feedback
Suspend
End Block

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AAGCTATGGGAGTGGTGGTAGCAACTGGAGTTAAACCGAAATT
GGCAAGATCCGGGATGAAATGGTGGCAACAGAACAGGAAGAA
CACCCCTTCAGCAAAAACTAGATGAATTTGGGGAACAGCTTTCC
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGACTTCAATGACCCGGTTCATGGAGgtcmgatcagaggtgctatttacta
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ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'
```

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Which of the following is the most likely effect of this mutation?

○ A. Decreased mRNA export to the cytosol

○ B. Impaired ribosomal attachment to mRNA

○ C. Incorrect splicing of pre-mRNA

○ D. Increased degradation of mRNA by 5' exonucleases

○ E. Translation of the 3'-untranslated region of mRNA

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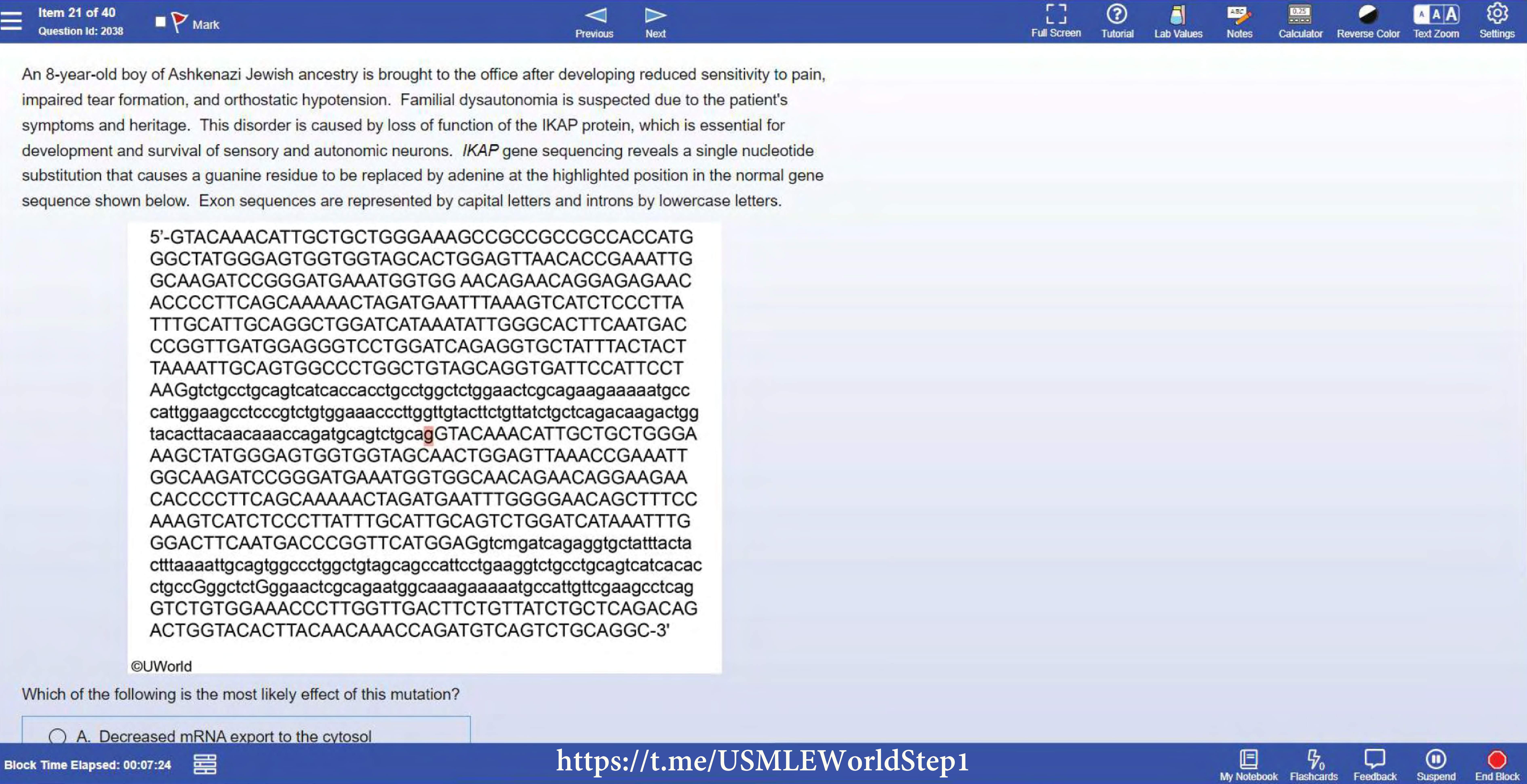
Item 21 of 40
Question Id: 2038
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 8-year-old boy of Ashkenazi Jewish ancestry is brought to the office after developing reduced sensitivity to pain, impaired tear formation, and orthostatic hypotension. Familial dysautonomia is suspected due to the patient's symptoms and heritage. This disorder is caused by loss of function of the IKAP protein, which is essential for development and survival of sensory and autonomic neurons. *IKAP* gene sequencing reveals a single nucleotide substitution that causes a guanine residue to be replaced by adenine at the highlighted position in the normal gene sequence shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAAACTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCCTGGATCAGAGGTGCTATTTACTACT
TAAAATTGCAGTGGCCCTGGCTGTAGCAGGTGATTCCATTCCT
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tacacttacaacaaaccagatgcagtctgcagGTACAAACATTGCTGCTGGGA
AAGCTATGGGAGTGGTGGTAGCAACTGGAGTTAAACCGAAATT
GGCAAGATCCGGGATGAAATGGTGGCAACAGAACAGGAAGAA
CACCCCTTCAGCAAAAACTAGATGAATTTGGGGAACAGCTTTCC
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGACTTCAATGACCCGGTTCATGGAGgtcmgatcagaggtgctatttacta
ctttaaaattgcagtggccctggctgtagcagccattcctgaaggtctgcctgcagtcatcacac
ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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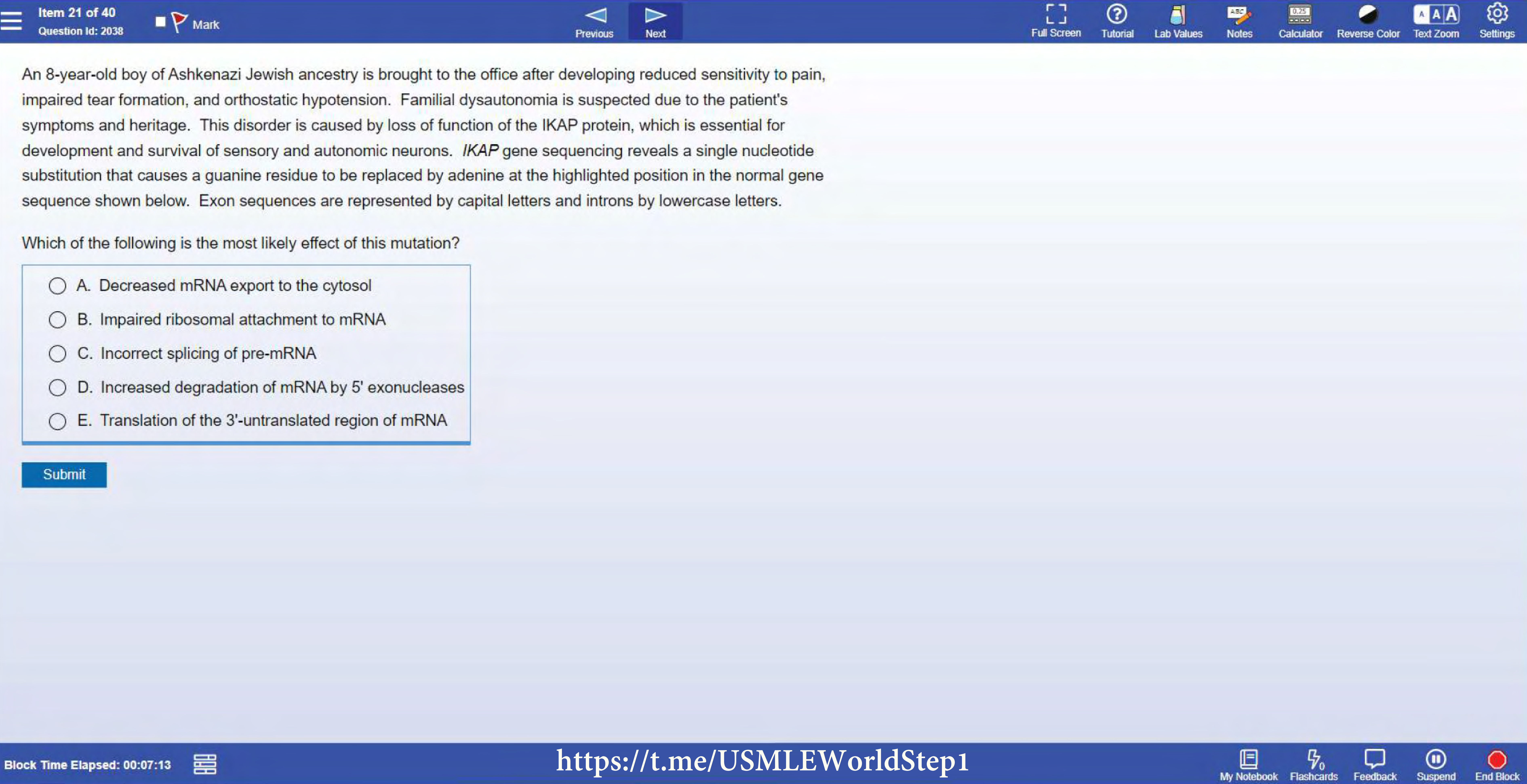
Which of the following is the most likely effect of this mutation?

○ A. Decreased mRNA export to the cytosol

Block Time Elapsed: 00:07:24
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 21 of 40
Question Id: 2038
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ C. Incorrect splicing of pre-mRNA
○ D. Increased degradation of mRNA by 5' exonucleases
○ E. Translation of the 3'-untranslated region of mRNA

Submit
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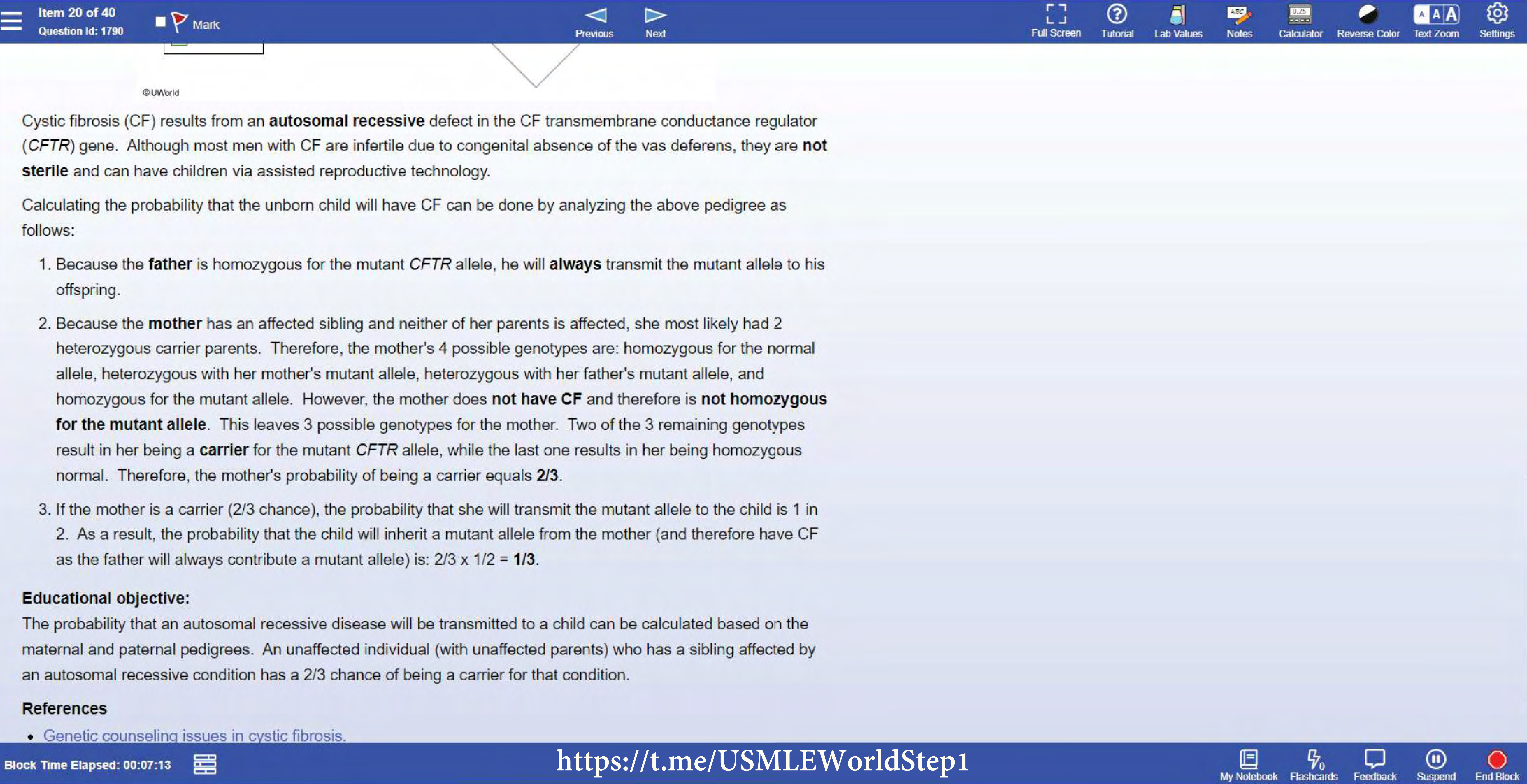
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 20 of 40
Question Id: 1790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Block Time Elapsed: 00:07:13
My Notebook
Flashcards
Feedback
Suspend
End Block

Cystic fibrosis (CF) results from an **autosomal recessive** defect in the CF transmembrane conductance regulator (*CFTR*) gene. Although most men with CF are infertile due to congenital absence of the vas deferens, they are **not sterile** and can have children via assisted reproductive technology.

Calculating the probability that the unborn child will have CF can be done by analyzing the above pedigree as follows:

1. Because the **father** is homozygous for the mutant *CFTR* allele, he will **always** transmit the mutant allele to his offspring.
2. Because the **mother** has an affected sibling and neither of her parents is affected, she most likely had 2 heterozygous carrier parents. Therefore, the mother's 4 possible genotypes are: homozygous for the normal allele, heterozygous with her mother's mutant allele, heterozygous with her father's mutant allele, and homozygous for the mutant allele. However, the mother does **not have CF** and therefore is **not homozygous for the mutant allele**. This leaves 3 possible genotypes for the mother. Two of the 3 remaining genotypes result in her being a **carrier** for the mutant *CFTR* allele, while the last one results in her being homozygous normal. Therefore, the mother's probability of being a carrier equals **2/3**.
3. If the mother is a carrier (2/3 chance), the probability that she will transmit the mutant allele to the child is 1 in 2. As a result, the probability that the child will inherit a mutant allele from the mother (and therefore have CF as the father will always contribute a mutant allele) is: 2/3 x 1/2 = **1/3**.

Educational objective:

The probability that an autosomal recessive disease will be transmitted to a child can be calculated based on the maternal and paternal pedigrees. An unaffected individual (with unaffected parents) who has a sibling affected by an autosomal recessive condition has a 2/3 chance of being a carrier for that condition.

References

- Genetic counseling issues in cystic fibrosis.

Explanation

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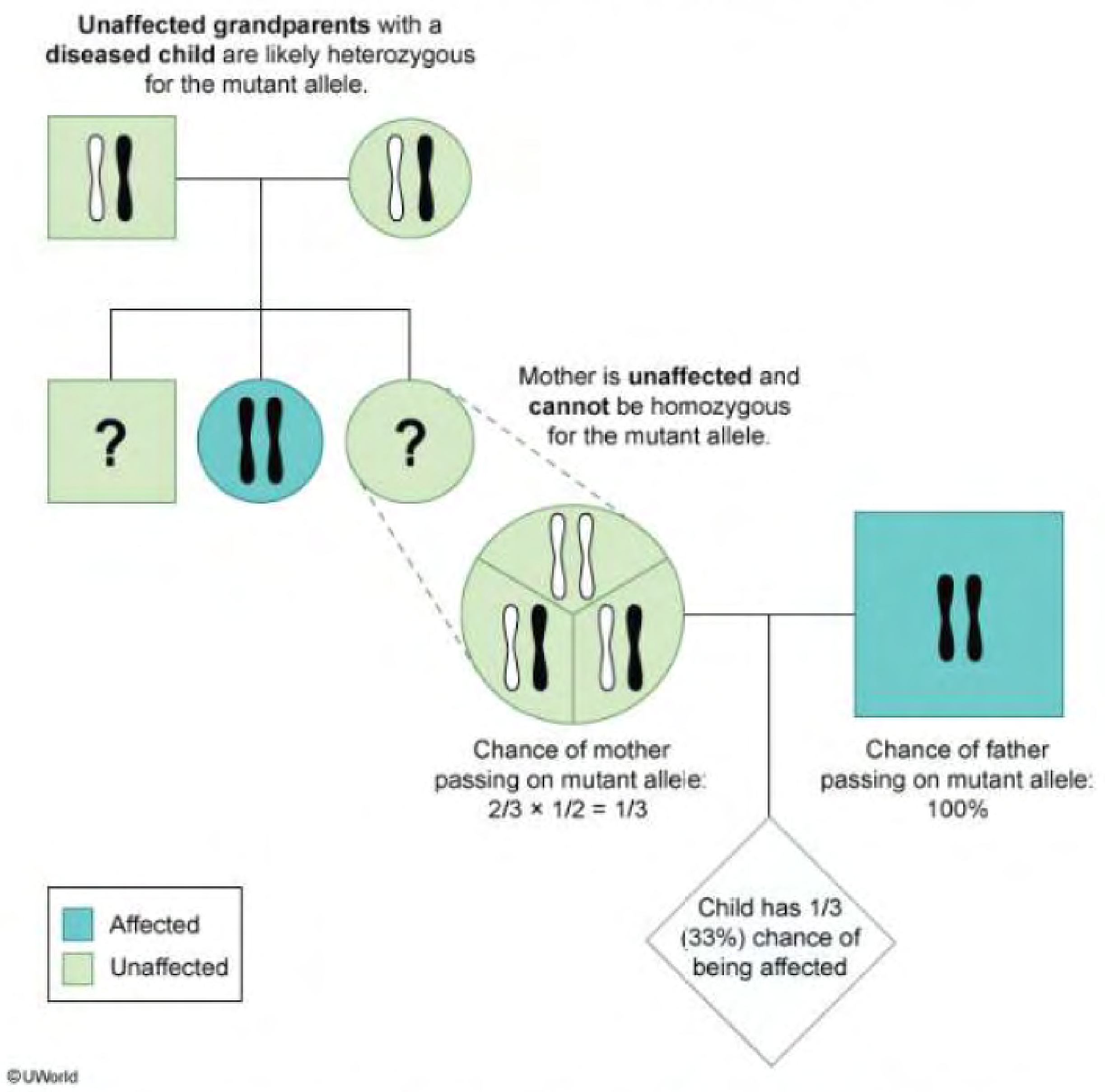
Probability of the child having cystic fibrosis


Unaffected grandparents with a **diseased child** are likely heterozygous for the mutant allele.
?
?
Mother is **unaffected** and **cannot** be homozygous for the mutant allele.
Chance of mother passing on mutant allele: 2/3 × 1/2 = 1/3
Chance of father passing on mutant allele: 100%
Child has 1/3 (33%) chance of being affected
Affected
Unaffected
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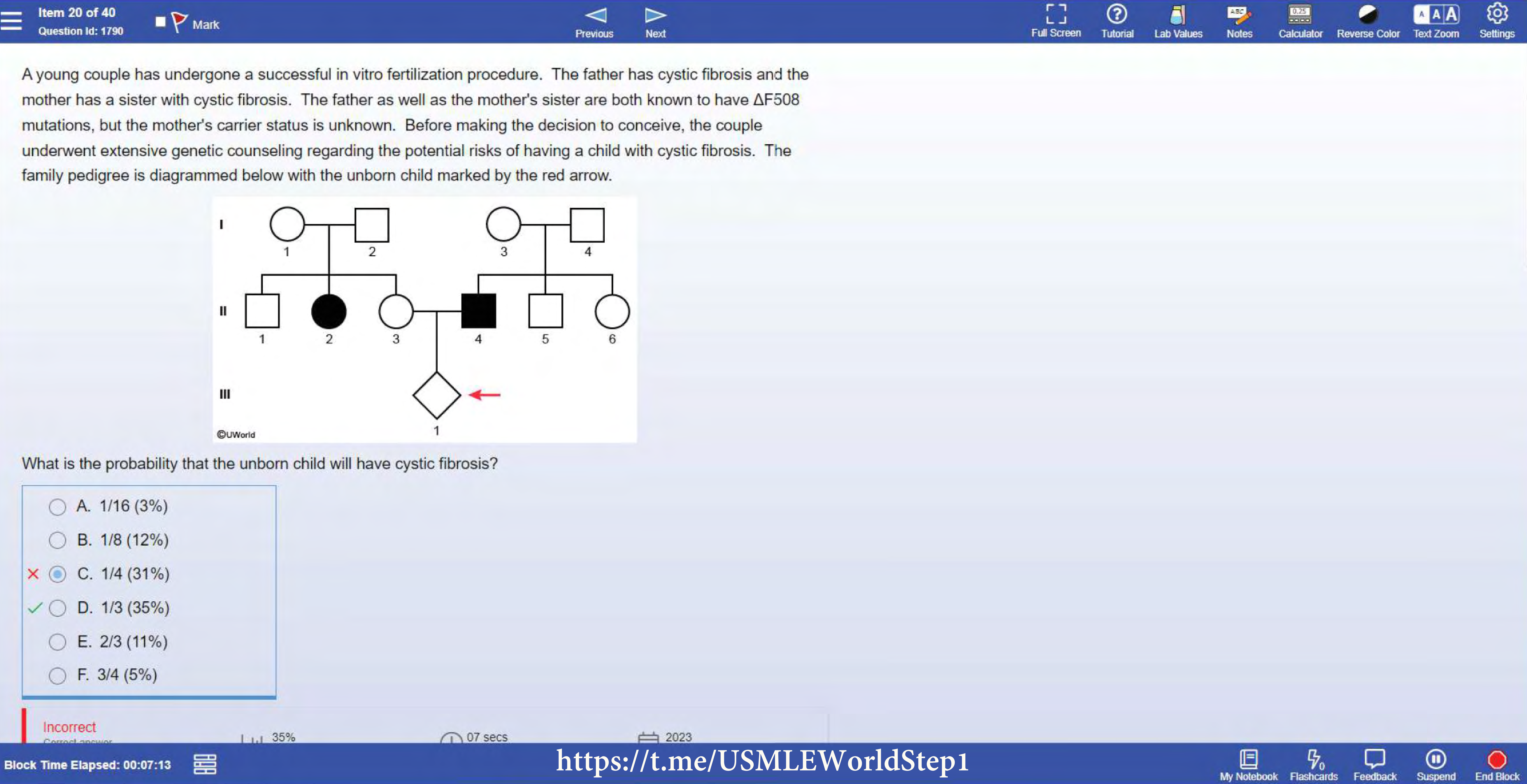
Item 20 of 40
Question Id: 1790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have ΔF508 mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.

I
1
2
3
4
II
1
2
3
4
5
6
III
1
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What is the probability that the unborn child will have cystic fibrosis?

- ○ A. 1/16 (3%)
- ○ B. 1/8 (12%)
- ✗ ● C. 1/4 (31%)
- ✓ ○ D. 1/3 (35%)
- ○ E. 2/3 (11%)
- ○ F. 3/4 (5%)

Incorrect
Correct answer
35%
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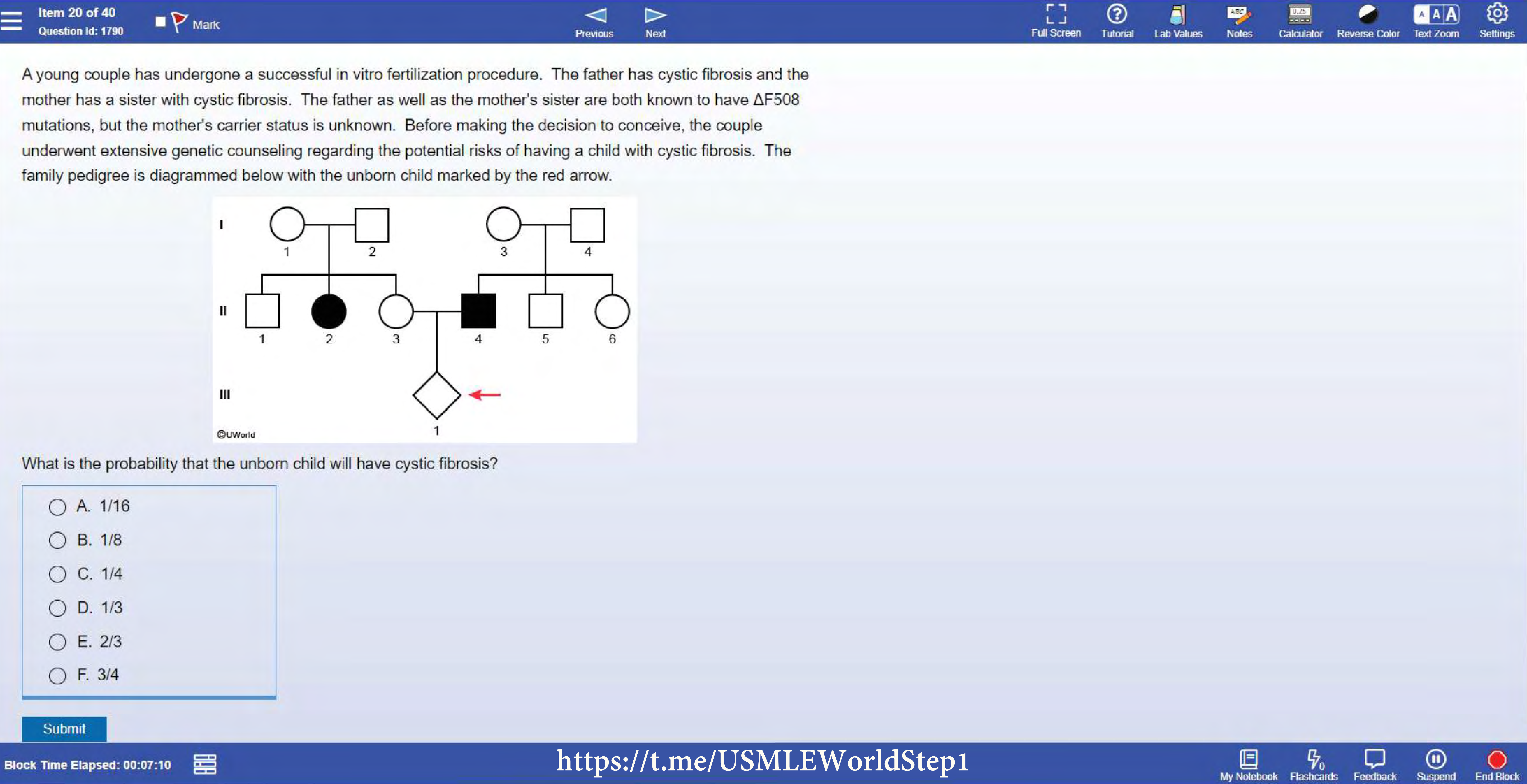

Item 20 of 40
Question Id: 1790
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have ΔF508 mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.

I
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What is the probability that the unborn child will have cystic fibrosis?

○ A. 1/16

○ B. 1/8

○ C. 1/4

○ D. 1/3

○ E. 2/3

○ F. 3/4

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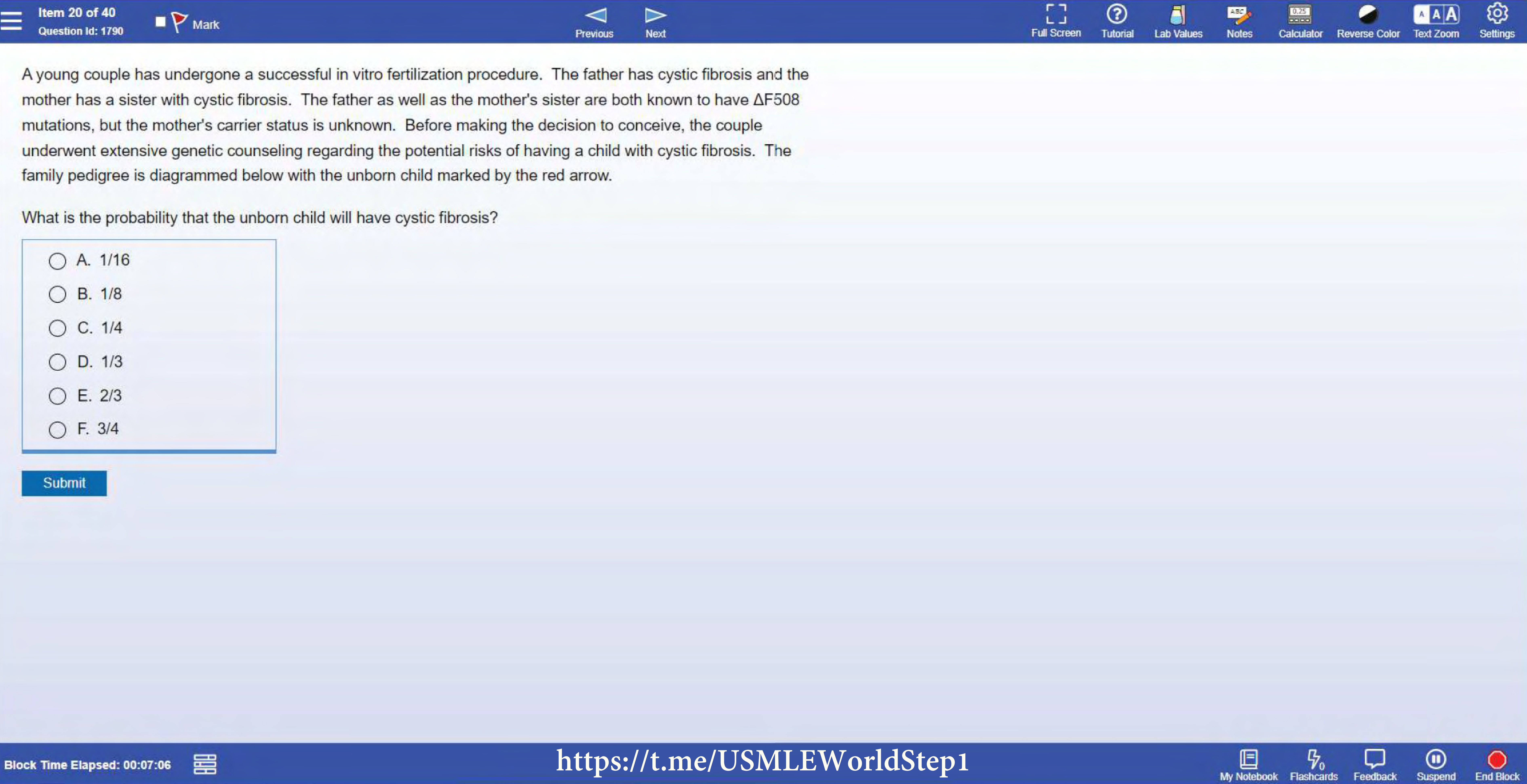
Item 20 of 40
Question Id: 1790
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have ΔF508 mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.

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- ○ A. 1/16
- ○ B. 1/8
- ○ C. 1/4
- ○ D. 1/3
- ○ E. 2/3
- ○ F. 3/4

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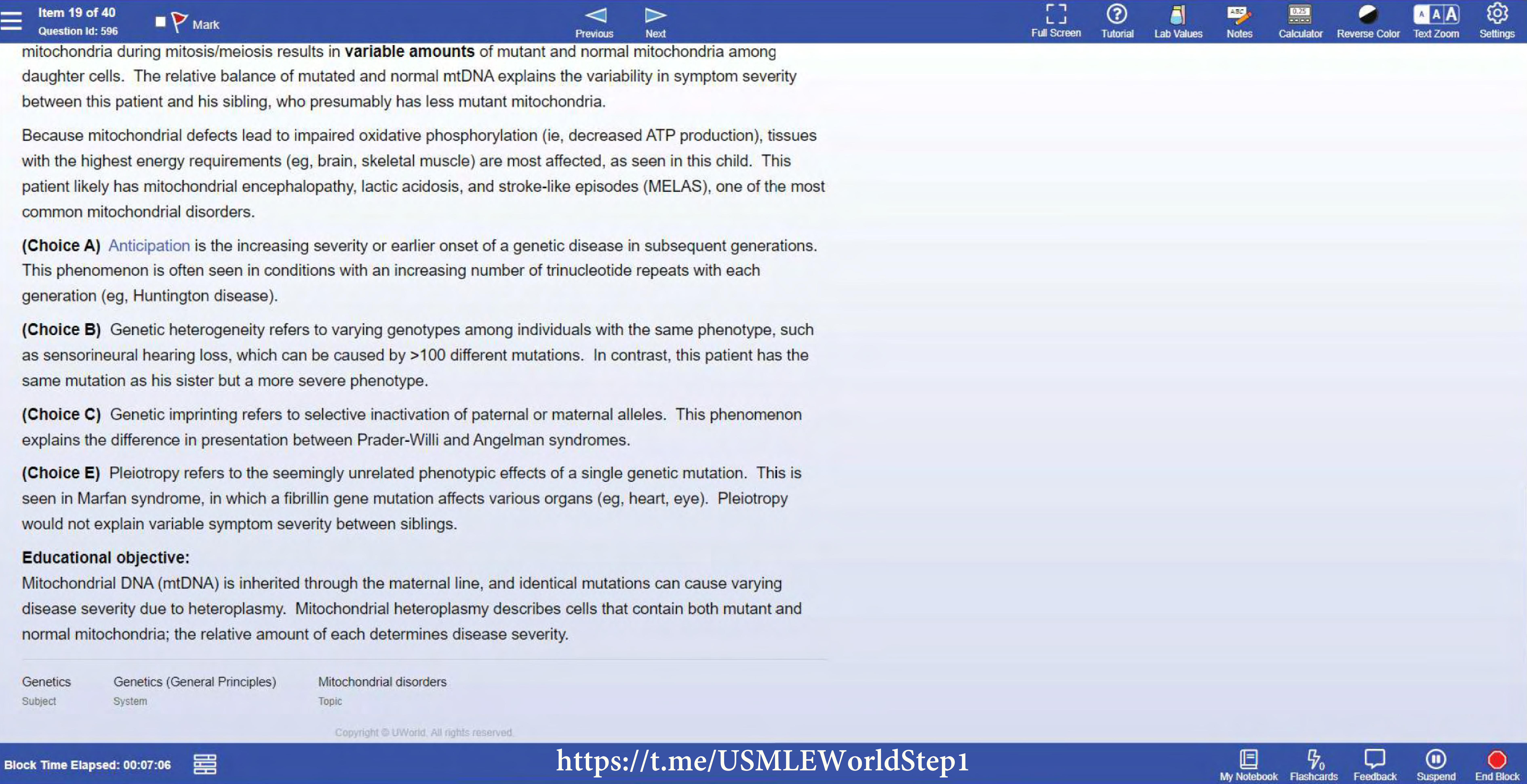

mitochondria during mitosis/meiosis results in **variable amounts** of mutant and normal mitochondria among daughter cells. The relative balance of mutated and normal mtDNA explains the variability in symptom severity between this patient and his sibling, who presumably has less mutant mitochondria.

Because mitochondrial defects lead to impaired oxidative phosphorylation (ie, decreased ATP production), tissues with the highest energy requirements (eg, brain, skeletal muscle) are most affected, as seen in this child. This patient likely has mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), one of the most common mitochondrial disorders.

(Choice A) Anticipation is the increasing severity or earlier onset of a genetic disease in subsequent generations. This phenomenon is often seen in conditions with an increasing number of trinucleotide repeats with each generation (eg, Huntington disease).

(Choice B) Genetic heterogeneity refers to varying genotypes among individuals with the same phenotype, such as sensorineural hearing loss, which can be caused by >100 different mutations. In contrast, this patient has the same mutation as his sister but a more severe phenotype.

(Choice C) Genetic imprinting refers to selective inactivation of paternal or maternal alleles. This phenomenon explains the difference in presentation between Prader-Willi and Angelman syndromes.

(Choice E) Pleiotropy refers to the seemingly unrelated phenotypic effects of a single genetic mutation. This is seen in Marfan syndrome, in which a fibrillin gene mutation affects various organs (eg, heart, eye). Pleiotropy would not explain variable symptom severity between siblings.

Educational objective:

Mitochondrial DNA (mtDNA) is inherited through the maternal line, and identical mutations can cause varying disease severity due to heteroplasmy. Mitochondrial heteroplasmy describes cells that contain both mutant and normal mitochondria; the relative amount of each determines disease severity.

Genetics	Genetics (General Principles)	Mitochondrial disorders
Subject	System	Topic

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Inheritance of mtDNA mutations affects male and female offspring with equal frequency, but disease often presents

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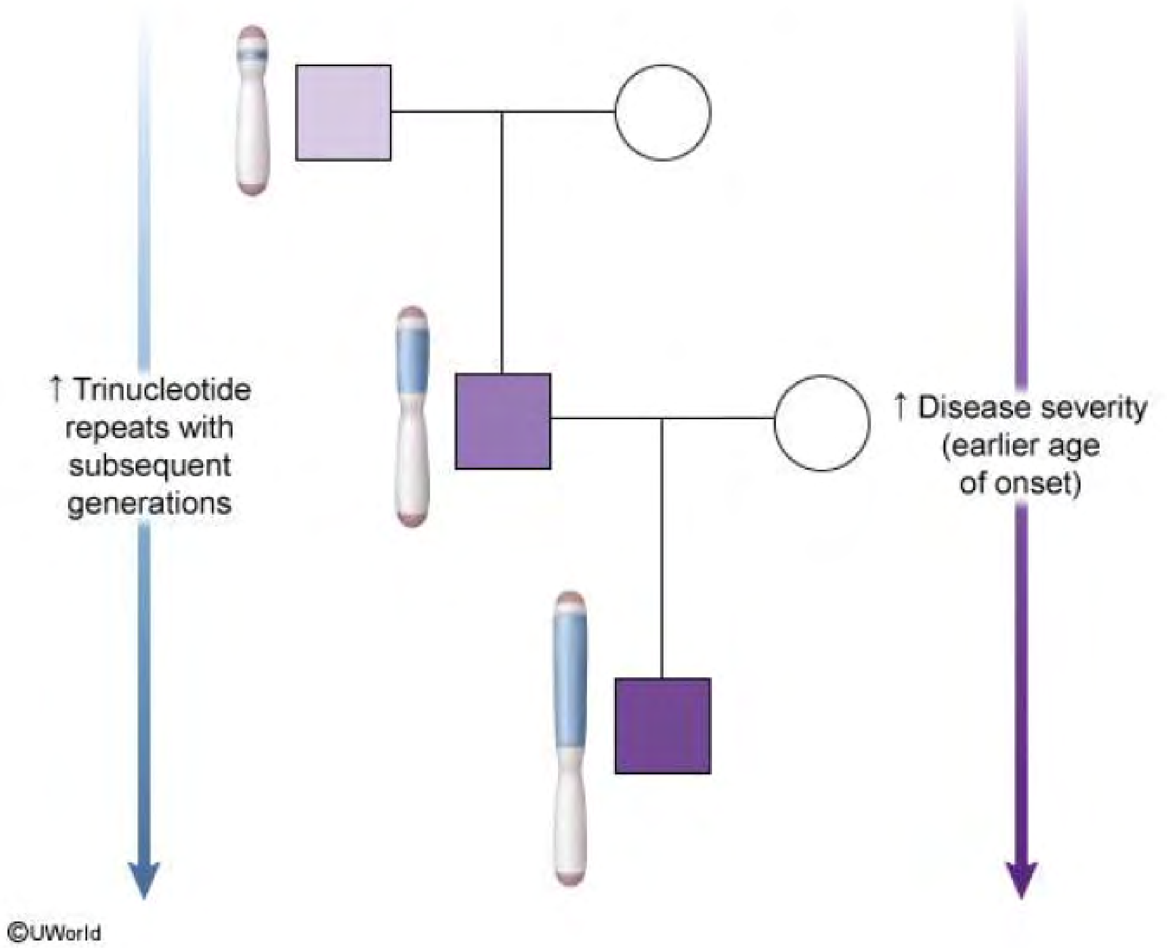
Genetic anticipation


↑ Trinucleotide repeats with subsequent generations
↑ Disease severity (earlier age of onset)
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disease severity due to heteroplasmy. Mitochondrial heteroplasmy describes cells that contain both mutant and

normal mitochondria; the relative amount of each determines disease severity.

This patient has a genetic condition with a **maternal inheritance pattern**, a finding characteristic of mitochondrial
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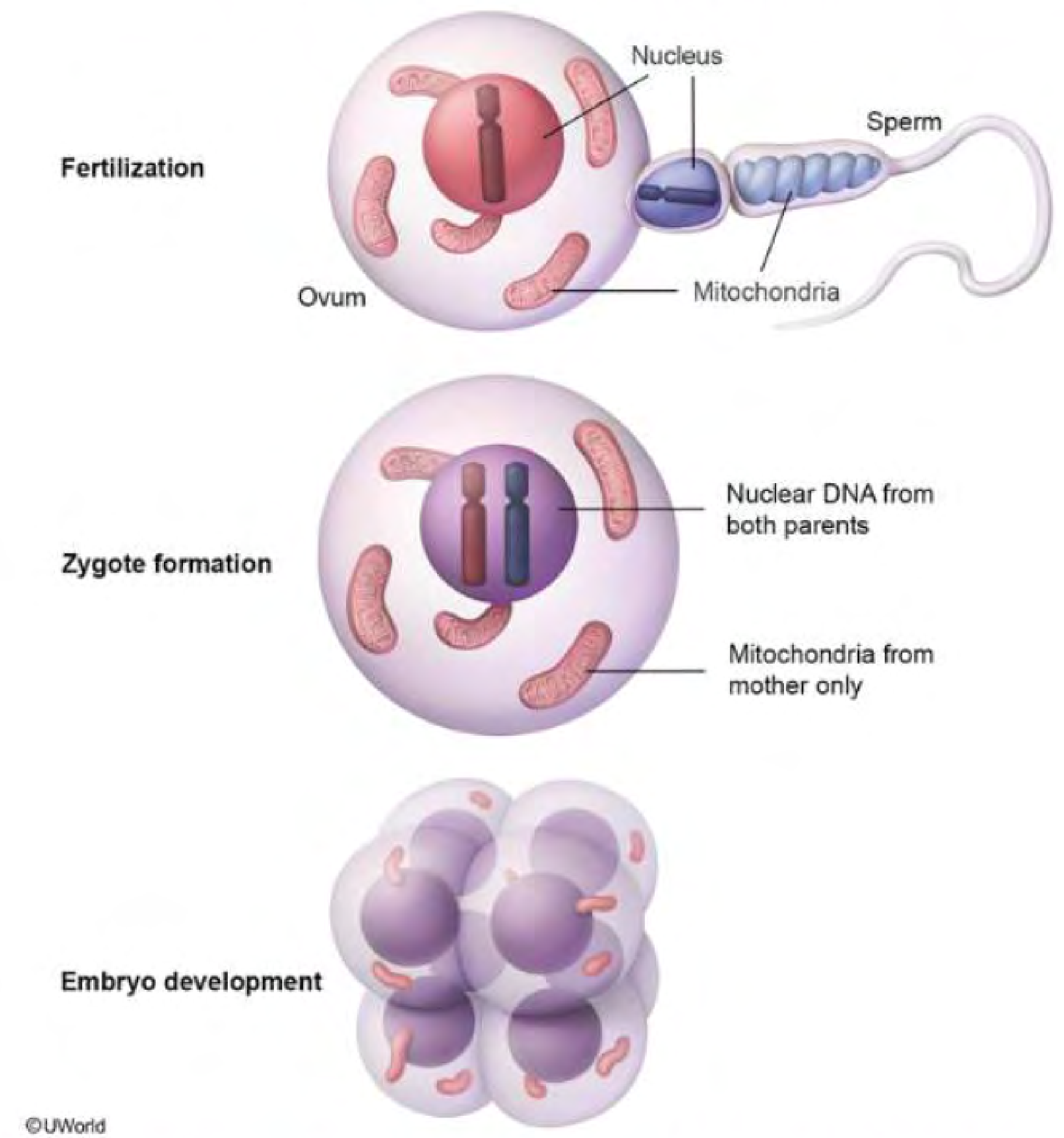
Maternal inheritance of mitochondrial DNA


Fertilization
Nucleus
Sperm
Ovum
Mitochondria
Zygote formation
Nuclear DNA from both parents
Mitochondria from mother only
Embryo development

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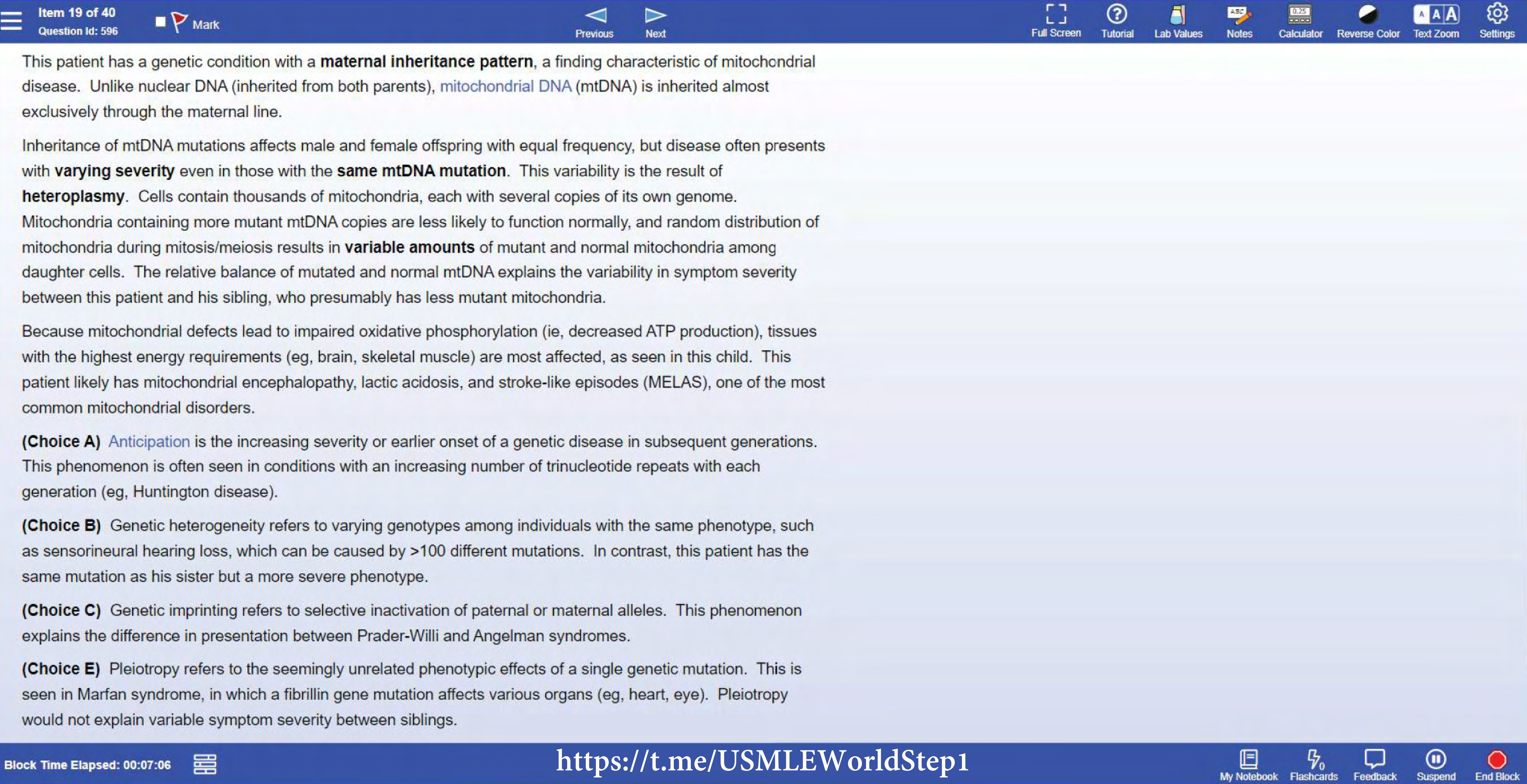

This patient has a genetic condition with a **maternal inheritance pattern**, a finding characteristic of mitochondrial disease. Unlike nuclear DNA (inherited from both parents), mitochondrial DNA (mtDNA) is inherited almost exclusively through the maternal line.

Inheritance of mtDNA mutations affects male and female offspring with equal frequency, but disease often presents with **varying severity** even in those with the **same mtDNA mutation**. This variability is the result of **heteroplasmy**. Cells contain thousands of mitochondria, each with several copies of its own genome. Mitochondria containing more mutant mtDNA copies are less likely to function normally, and random distribution of mitochondria during mitosis/meiosis results in **variable amounts** of mutant and normal mitochondria among daughter cells. The relative balance of mutated and normal mtDNA explains the variability in symptom severity between this patient and his sibling, who presumably has less mutant mitochondria.

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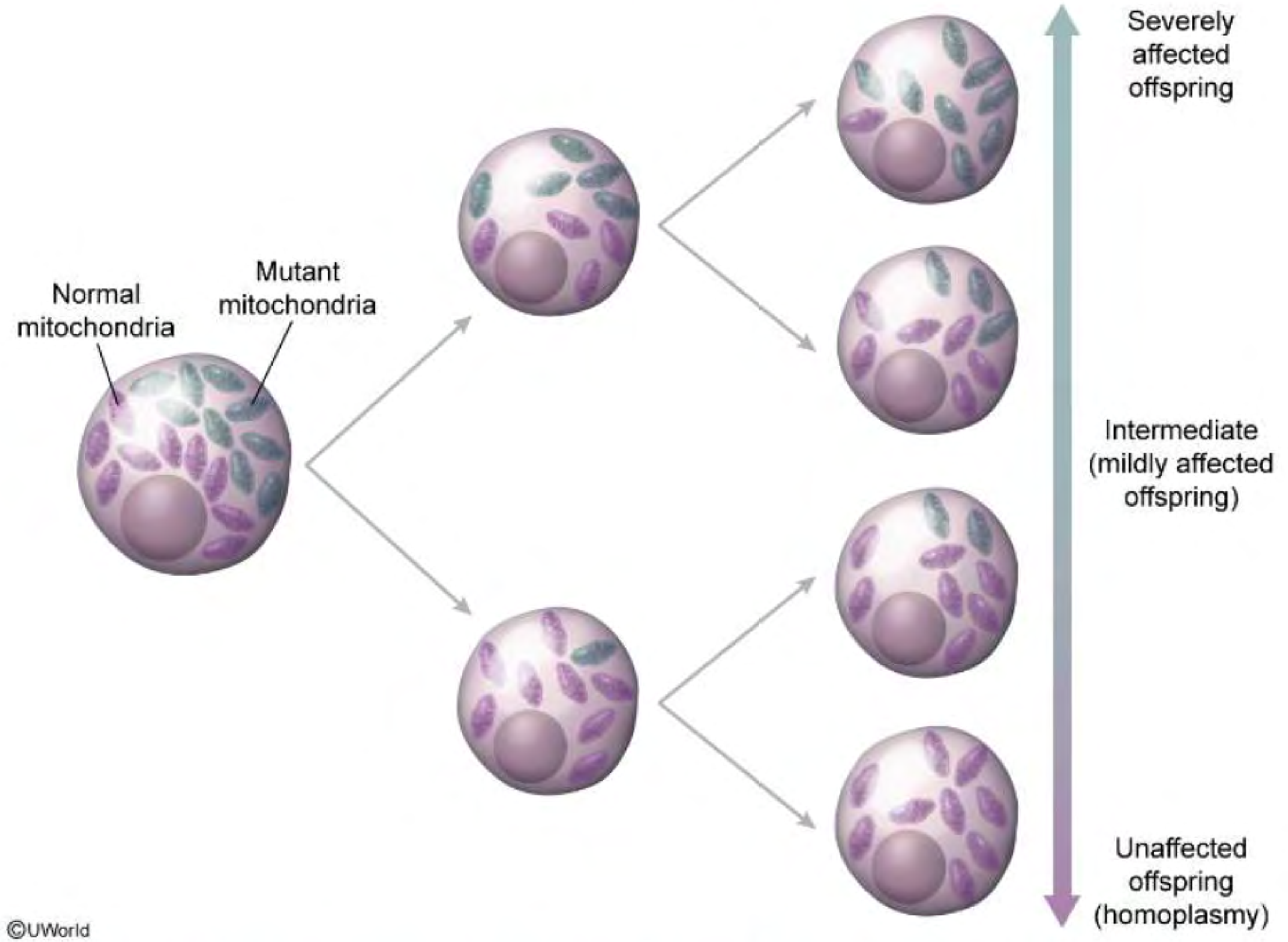
Exhibit Display

Heteroplasmy


Normal mitochondria
Mutant mitochondria
Severely affected offspring
Intermediate (mildly affected offspring)
Unaffected offspring (homoplasmy)

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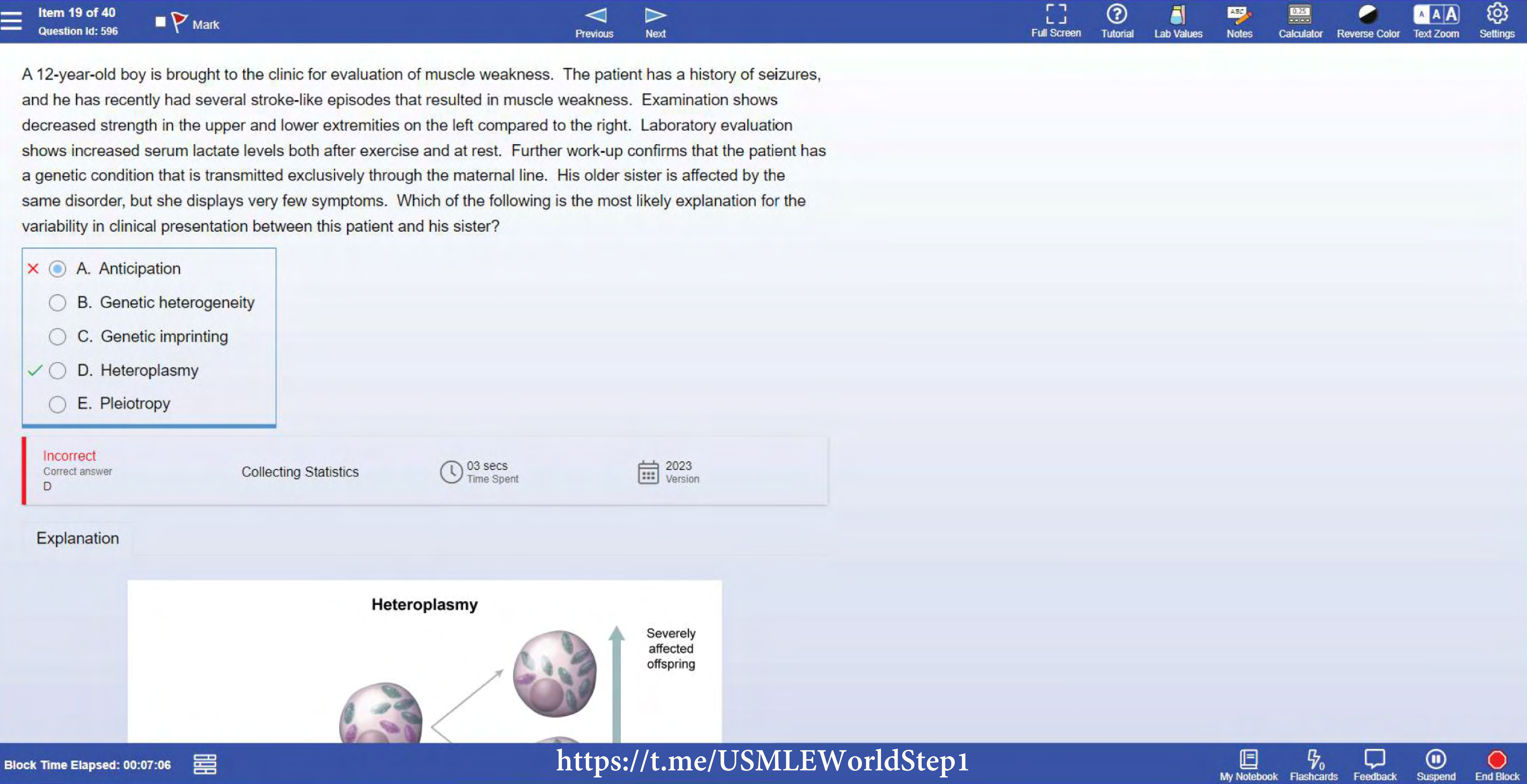
Mitochondria containing more mutant mtDNA copies are less likely to function normally, and random distribution of


Item 19 of 40
Question Id: 596
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 12-year-old boy is brought to the clinic for evaluation of muscle weakness. The patient has a history of seizures, and he has recently had several stroke-like episodes that resulted in muscle weakness. Examination shows decreased strength in the upper and lower extremities on the left compared to the right. Laboratory evaluation shows increased serum lactate levels both after exercise and at rest. Further work-up confirms that the patient has a genetic condition that is transmitted exclusively through the maternal line. His older sister is affected by the same disorder, but she displays very few symptoms. Which of the following is the most likely explanation for the variability in clinical presentation between this patient and his sister?

- ✗ ● A. Anticipation
- ○ B. Genetic heterogeneity
- ○ C. Genetic imprinting
- ✓ ○ D. Heteroplasmy
- ○ E. Pleiotropy

Incorrect
Correct answer
D

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Explanation

Heteroplasmy

Severely affected offspring
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Feedback
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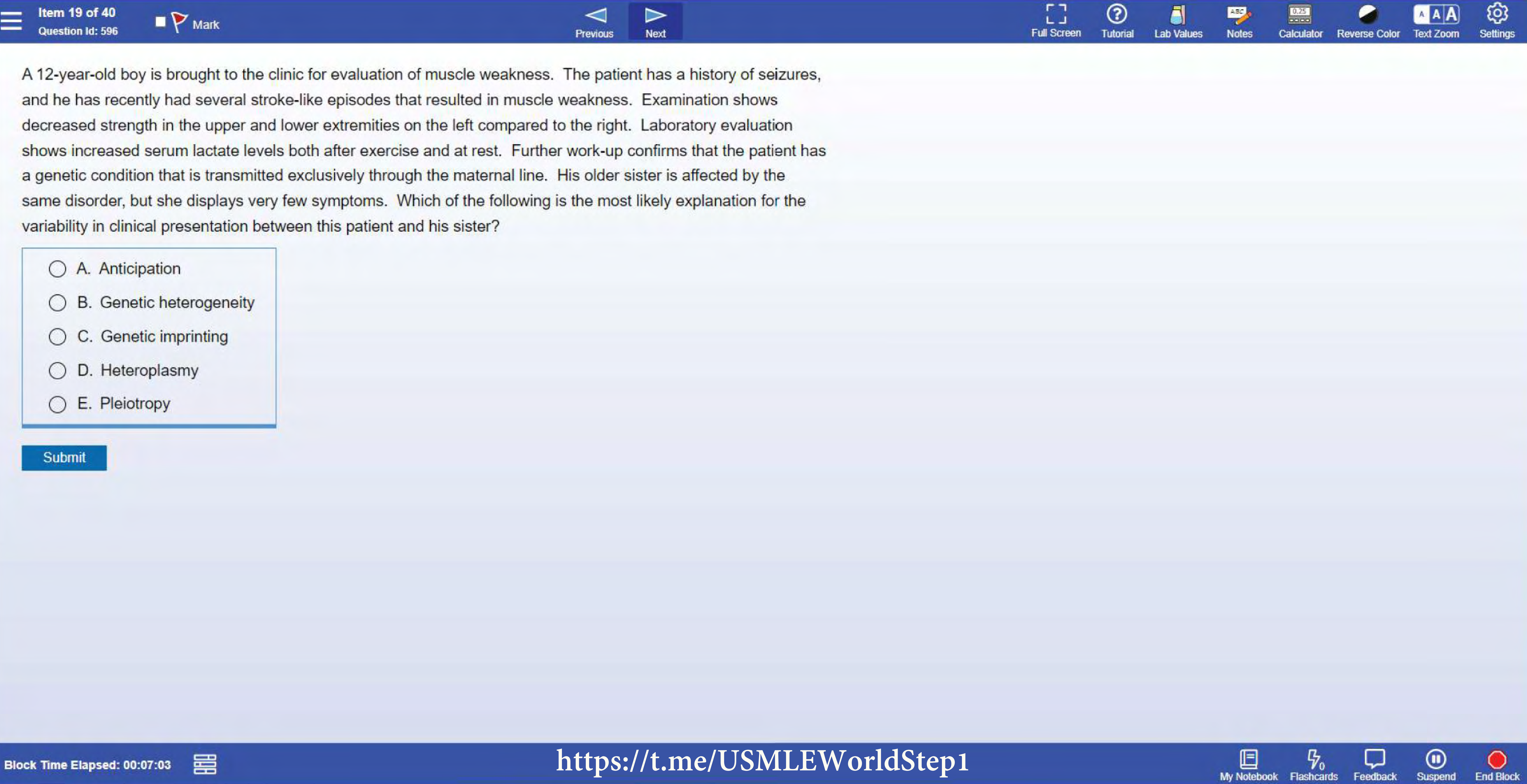
Item 19 of 40
Question Id: 596
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
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Text Zoom
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- ○ C. Genetic imprinting
- ○ D. Heteroplasmy
- ○ E. Pleiotropy

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Flashcards
Feedback
Suspend
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MCAD = medium-chain acyl-CoA dehydrogenase; **TCA** = tricarboxylic acid.
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This p... developed **hypoketotic hypoglycemia** after fasting, which is consistent with a **defect in fatty acid**

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bodies. Acyl-CoA dehydrogenase catalyzes the first step in the beta-oxidation pathway and is the most commonly deficient enzyme.

References

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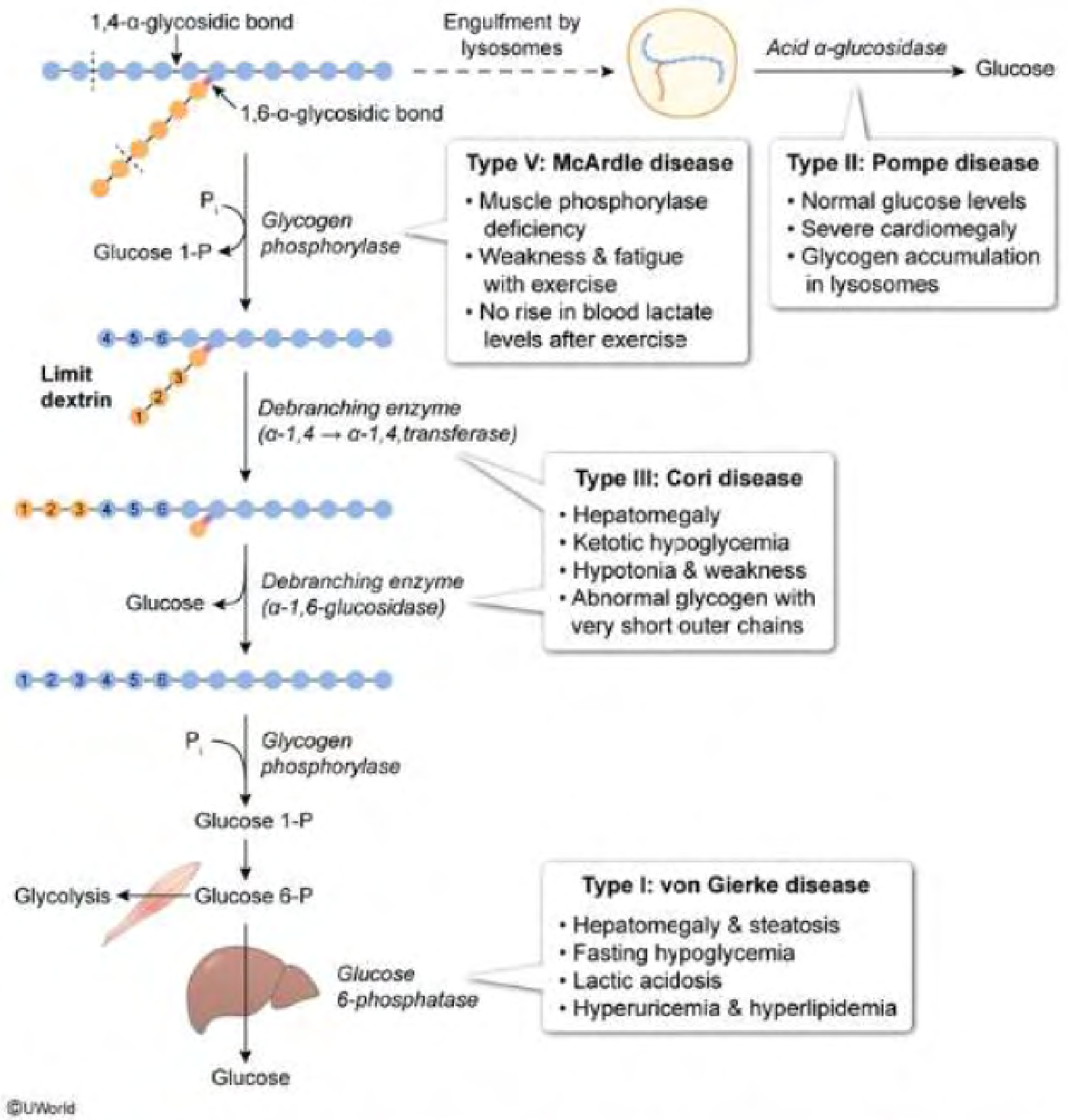
Impairments in glycogenolysis


1,4-α-glycosidic bond
Engulfment by lysosomes
Acid α-glucosidase
Glucose
1,6-α-glycosidic bond
Pᵢ
Glucose 1-P
Glycogen phosphorylase
4 5 6
Limit dextrin
3 2 1
Debranching enzyme (α-1,4 → α-1,4,transferase)
1 2 3 4 5 6
Glucose
Debranching enzyme (α-1,6-glucosidase)
1 2 3 4 5 6
Pᵢ
Glycogen phosphorylase
Glucose 1-P
Glycolysis
Glucose 6-P
Glucose 6-phosphatase
Glucose
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Type V: McArdle disease
- Muscle phosphorylase deficiency
- Weakness & fatigue with exercise
- No rise in blood lactate levels after exercise

Type II: Pompe disease
- Normal glucose levels
- Severe cardiomegaly
- Glycogen accumulation in lysosomes

Type III: Cori disease
- Hepatomegaly
- Ketotic hypoglycemia
- Hypotonia & weakness
- Abnormal glycogen with very short outer chains

Type I: von Gierke disease
- Hepatomegaly & steatosis
- Fasting hypoglycemia
- Lactic acidosis
- Hyperuricemia & hyperlipidemia

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MCAD = medium-chain acyl-CoA dehydrogenase; TCA = tricarboxylic acid.
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This patient developed **hypoketotic hypoglycemia** after fasting, which is consistent with a **defect in fatty acid beta-oxidation** in the mitochondria. Beta-oxidation of fatty acids yields $FADH_2$ and NADH for ATP production and generates acetyl-CoA for use in the citric acid cycle or ketone body production. **Ketone bodies** are an important energy source during periods of fasting; adults generally require more than 1-2 days of fasting before ketone use becomes substantial, whereas children have limited glucose reserves and begin using ketone bodies after as little as 8-10 hours.

Impaired beta-oxidation can be caused by a variety of enzymatic defects, the most common of which is **medium chain acyl-CoA dehydrogenase deficiency**. Affected individuals may remain asymptomatic for long periods until they experience a **significant fast**, during which they are unable to oxidize fatty acids to maintain glucose and ketone body production. Classic manifestations include hypoketotic hypoglycemia (eg, undetectable acetoacetate level), mild hepatomegaly, and liver dysfunction. Because the resulting metabolic crisis can have severe consequences (eg, seizures, sudden infant death), fatty acid oxidation disorders are part of standard newborn screening.

Treatment of acyl-CoA dehydrogenase deficiency consists of prevention of fat catabolism. This means avoiding prolonged fasting as well as promptly supplying **glucose** during periods of illness.

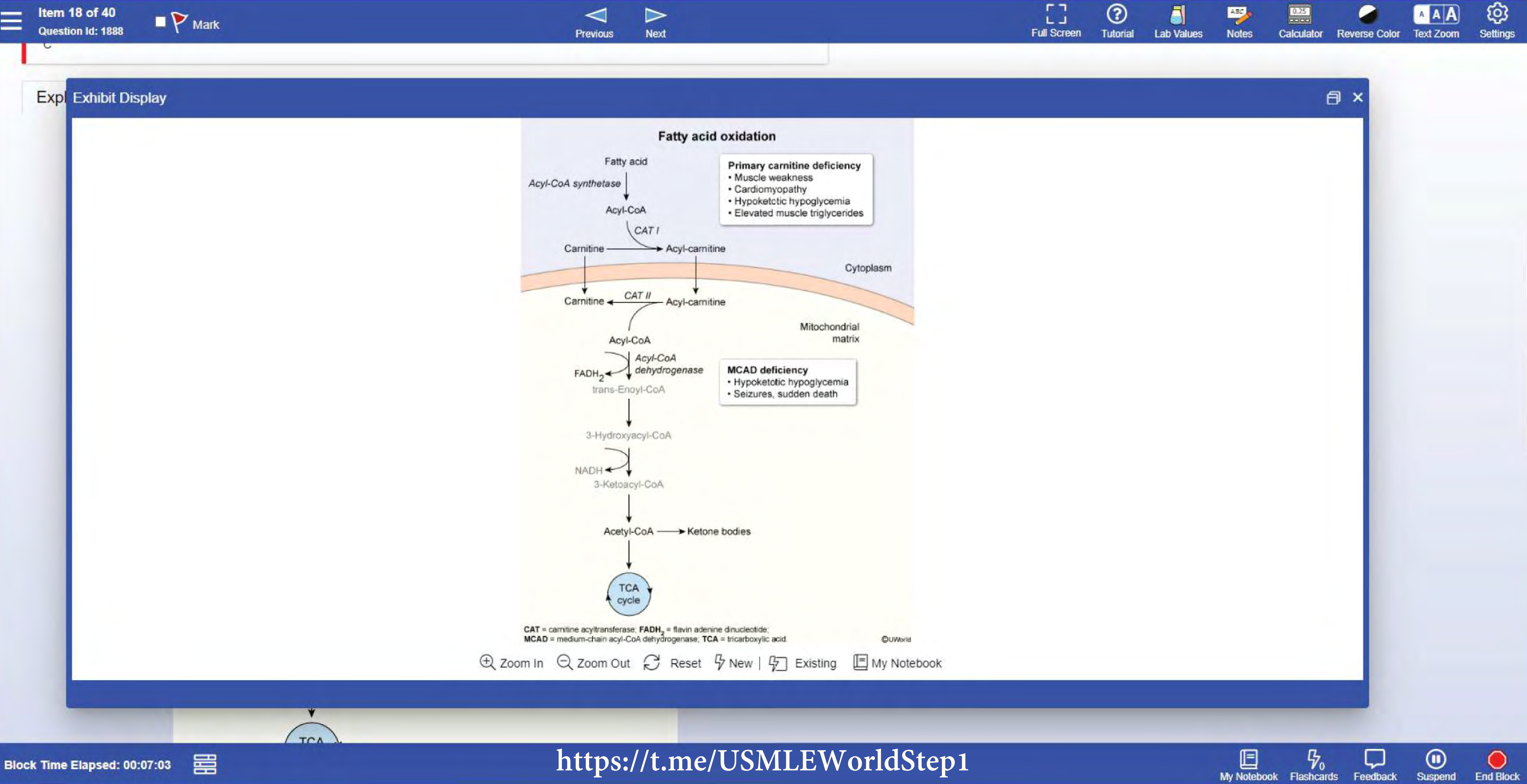
(Choice A) Acetyl-CoA carboxylase is the rate-limiting enzyme that catalyzes the first step in fatty acid synthesis. Acetyl-CoA carboxylase is normally suppressed during prolonged fasting.

(Choices B, D, and E) Acid alpha-glucosidase, glucose 6-phosphatase, and glycogen phosphorylase are involved in glycogenolysis. Deficiency of any of these enzymes can lead to glycogen storage disease. However, patients with glycogen storage disease have normal fatty acid oxidation and produce ketones during periods of fasting.

Educational objective:

Impaired beta-oxidation of fatty acids causes hypoglycemia after prolonged fasting and insufficient levels of ketone bodies. Acyl-CoA dehydrogenase catalyzes the first step in the beta-oxidation pathway and is the most commonly deficient enzyme.

References


Item 18 of 40
Question Id: 1888
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Fatty acid
Acyl-CoA synthetase
Acyl-CoA
CAT I
Carnitine
Acyl-carnitine
Cytoplasm
Carnitine
CAT II
Acyl-carnitine
Mitochondrial matrix
Acyl-CoA
Acyl-CoA dehydrogenase
$FADH_2$
trans-Enoyl-CoA
3-Hydroxyacyl-CoA
NADH
3-Ketoacyl-CoA
Acetyl-CoA
Ketone bodies
TCA cycle
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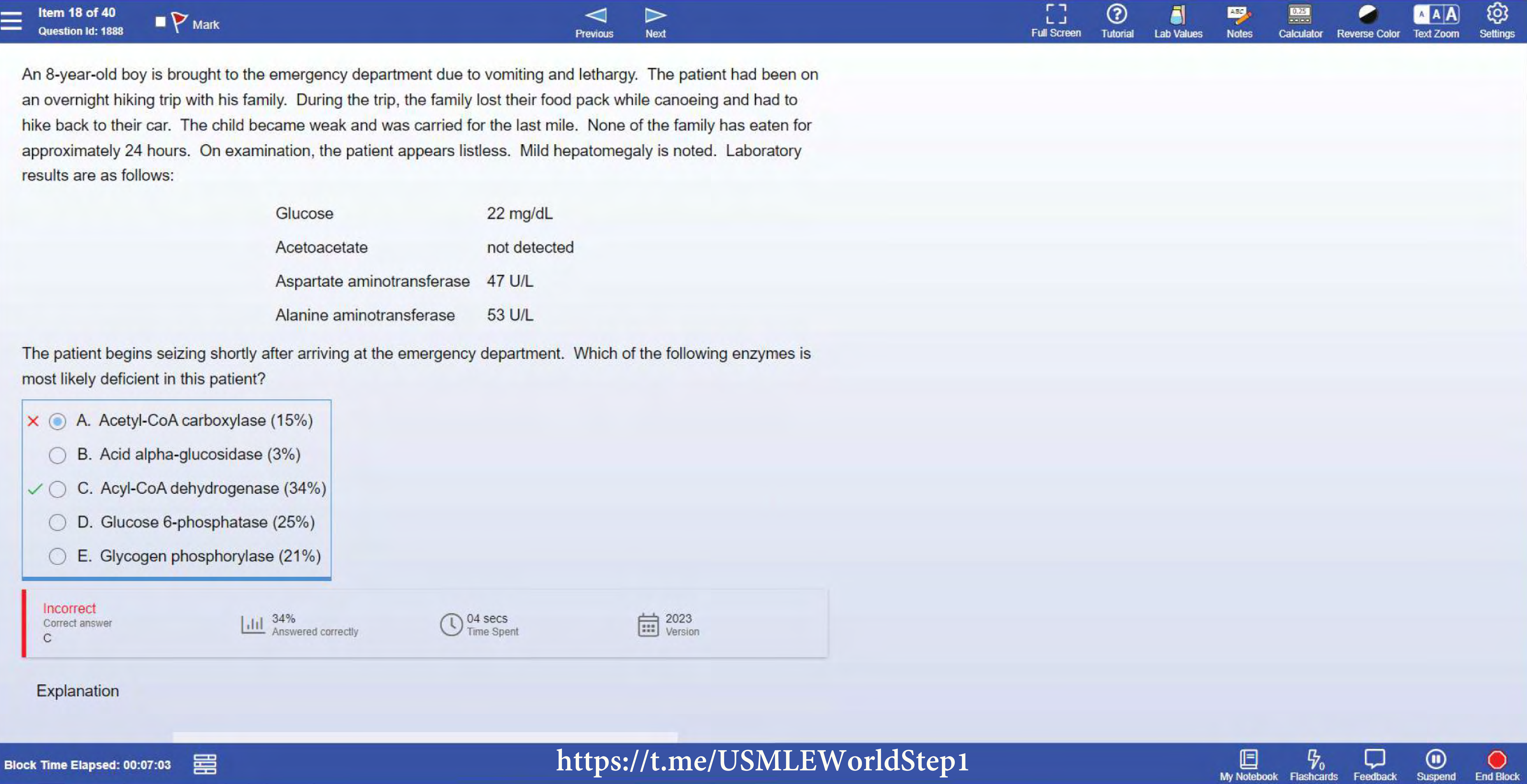
Zoom Out
Reset
New
Existing
My Notebook
TCA
Block Time Elapsed: 00:07:03
My Notebook
Flashcards
Feedback
Suspend
End Block

Fatty acid oxidation

Primary carnitine deficiency
- Muscle weakness
- Cardiomyopathy
- Hypoketotic hypoglycemia
- Elevated muscle triglycerides

MCAD deficiency
- Hypoketotic hypoglycemia
- Seizures, sudden death

CAT = carnitine acyltransferase; **$FADH_2$** = flavin adenine dinucleotide; **MCAD** = medium-chain acyl-CoA dehydrogenase; **TCA** = tricarboxylic acid


Item 18 of 40
Question Id: 1888
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 8-year-old boy is brought to the emergency department due to vomiting and lethargy. The patient had been on an overnight hiking trip with his family. During the trip, the family lost their food pack while canoeing and had to hike back to their car. The child became weak and was carried for the last mile. None of the family has eaten for approximately 24 hours. On examination, the patient appears listless. Mild hepatomegaly is noted. Laboratory results are as follows:

Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

- ✗ ● A. Acetyl-CoA carboxylase (15%)
- ○ B. Acid alpha-glucosidase (3%)
- ✓ ○ C. Acyl-CoA dehydrogenase (34%)
- ○ D. Glucose 6-phosphatase (25%)
- ○ E. Glycogen phosphorylase (21%)

Incorrect
Correct answer
C

34%
Answered correctly

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Flashcards
Feedback
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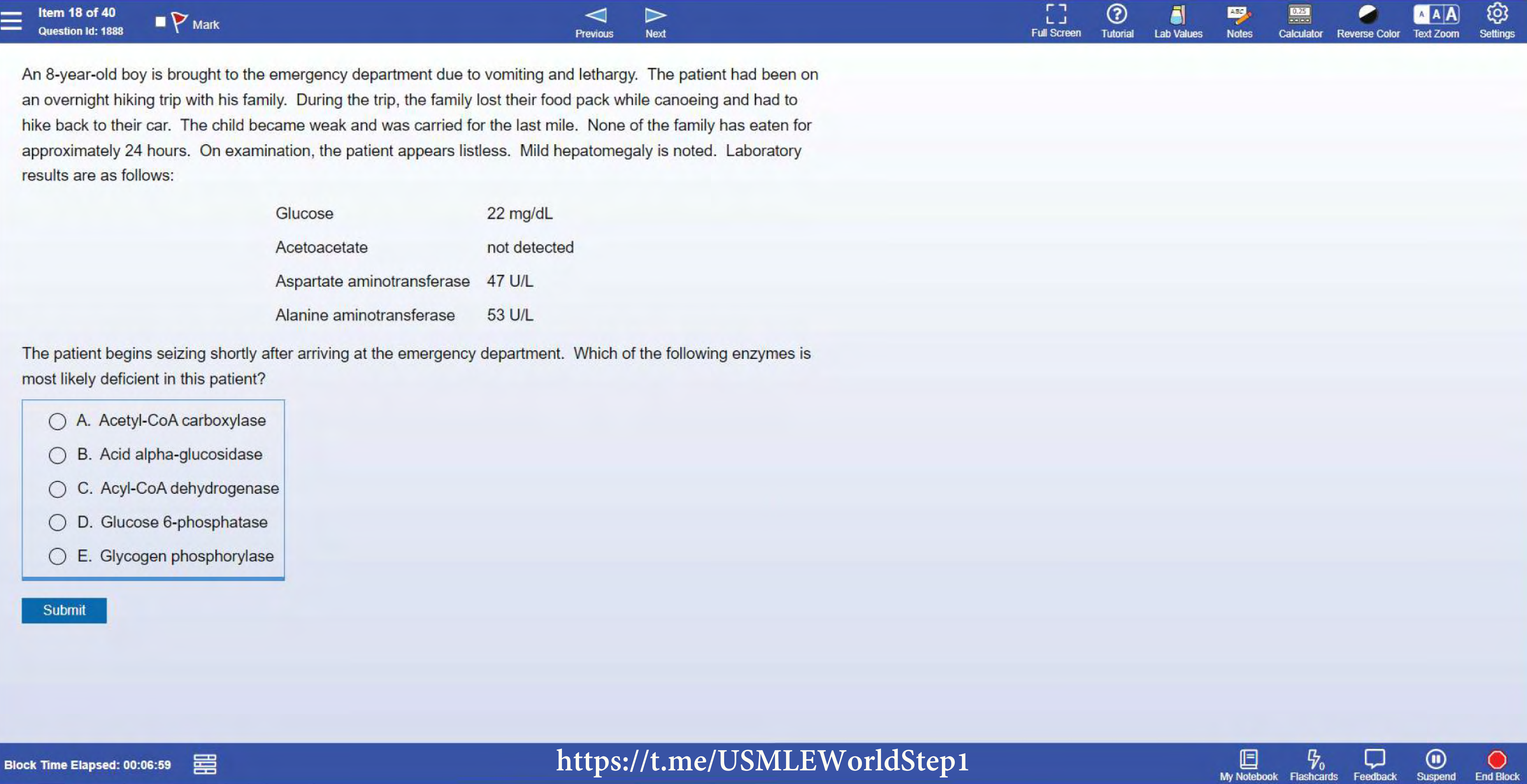
Item 18 of 40
Question Id: 1888
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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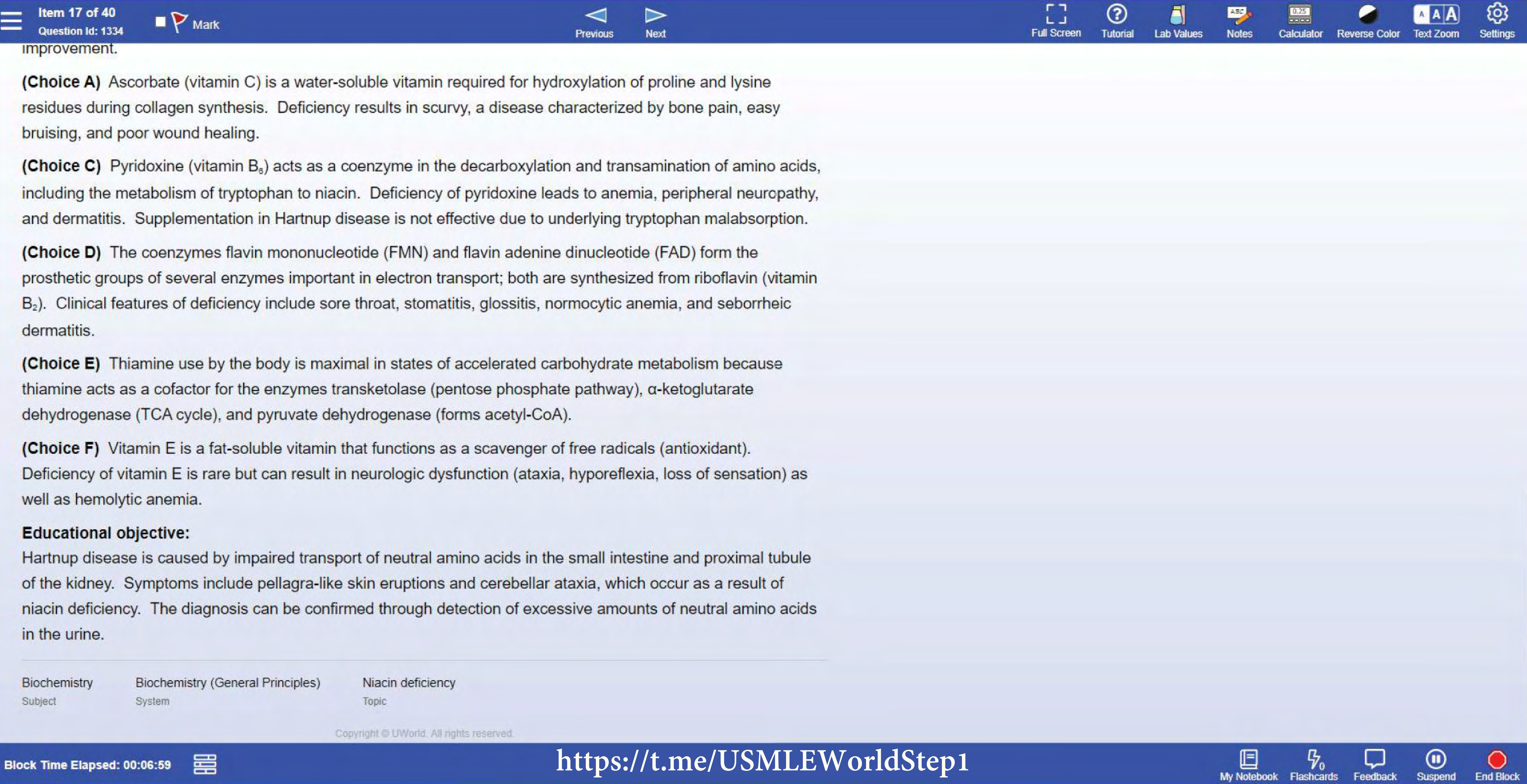
- ○ E. Glycogen phosphorylase



improvement.

(Choice A) Ascorbate (vitamin C) is a water-soluble vitamin required for hydroxylation of proline and lysine residues during collagen synthesis. Deficiency results in scurvy, a disease characterized by bone pain, easy bruising, and poor wound healing.

(Choice C) Pyridoxine (vitamin B$_6$) acts as a coenzyme in the decarboxylation and transamination of amino acids, including the metabolism of tryptophan to niacin. Deficiency of pyridoxine leads to anemia, peripheral neuropathy, and dermatitis. Supplementation in Hartnup disease is not effective due to underlying tryptophan malabsorption.

(Choice D) The coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) form the prosthetic groups of several enzymes important in electron transport; both are synthesized from riboflavin (vitamin B$_2$). Clinical features of deficiency include sore throat, stomatitis, glossitis, normocytic anemia, and seborrheic dermatitis.

(Choice E) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

(Choice F) Vitamin E is a fat-soluble vitamin that functions as a scavenger of free radicals (antioxidant). Deficiency of vitamin E is rare but can result in neurologic dysfunction (ataxia, hyporeflexia, loss of sensation) as well as hemolytic anemia.

Educational objective:
Hartnup disease is caused by impaired transport of neutral amino acids in the small intestine and proximal tubule of the kidney. Symptoms include pellagra-like skin eruptions and cerebellar ataxia, which occur as a result of niacin deficiency. The diagnosis can be confirmed through detection of excessive amounts of neutral amino acids in the urine.

Biochemistry	Biochemistry (General Principles)	Niacin deficiency
Subject	System	Topic

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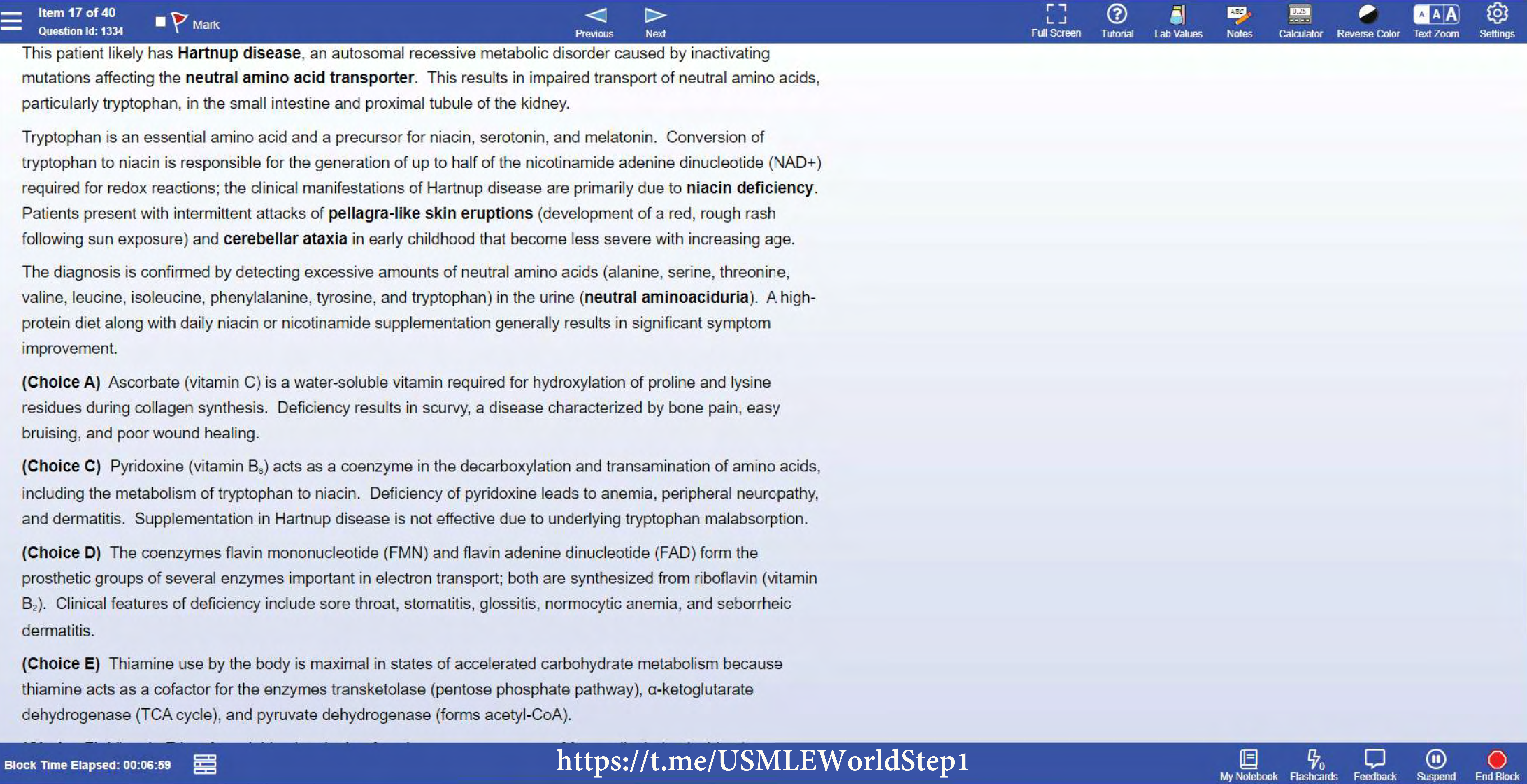

This patient likely has **Hartnup disease**, an autosomal recessive metabolic disorder caused by inactivating mutations affecting the **neutral amino acid transporter**. This results in impaired transport of neutral amino acids, particularly tryptophan, in the small intestine and proximal tubule of the kidney.

Tryptophan is an essential amino acid and a precursor for niacin, serotonin, and melatonin. Conversion of tryptophan to niacin is responsible for the generation of up to half of the nicotinamide adenine dinucleotide (NAD+) required for redox reactions; the clinical manifestations of Hartnup disease are primarily due to **niacin deficiency**. Patients present with intermittent attacks of **pellagra-like skin eruptions** (development of a red, rough rash following sun exposure) and **cerebellar ataxia** in early childhood that become less severe with increasing age.

The diagnosis is confirmed by detecting excessive amounts of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, and tryptophan) in the urine (**neutral aminoaciduria**). A high-protein diet along with daily niacin or nicotinamide supplementation generally results in significant symptom improvement.

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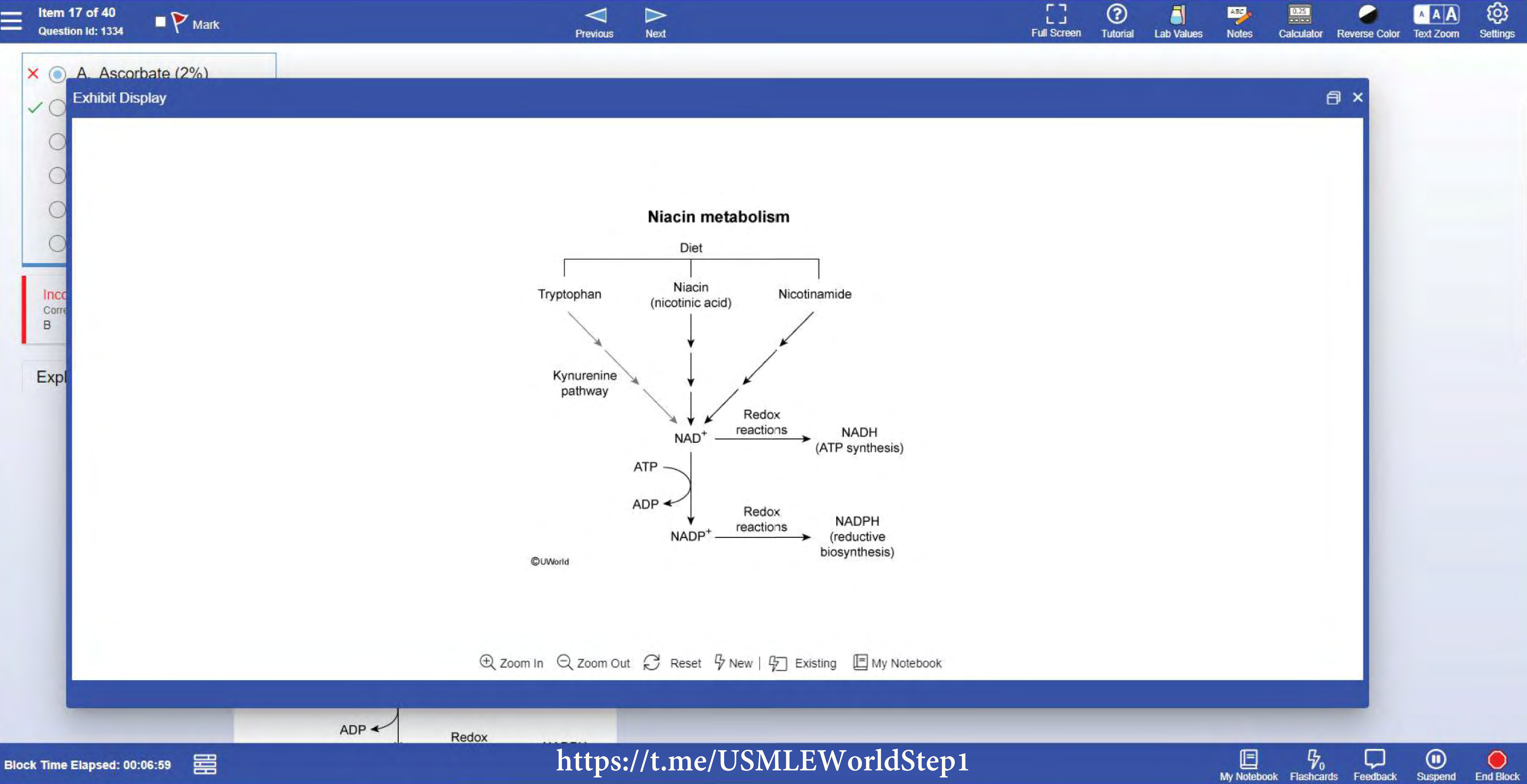

Item 17 of 40
Question Id: 1334
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:06:59
My Notebook
Flashcards
Feedback
Suspend
End Block

✗ ● A. Ascorbate (2%)

✓ ○

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Expl

Niacin metabolism

Diet
Tryptophan
Niacin
(nicotinic acid)
Nicotinamide
Kynurenine
pathway
NAD⁺
Redox
reactions
NADH
(ATP synthesis)
ATP
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NADP⁺
Redox
reactions
NADPH
(reductive
biosynthesis)

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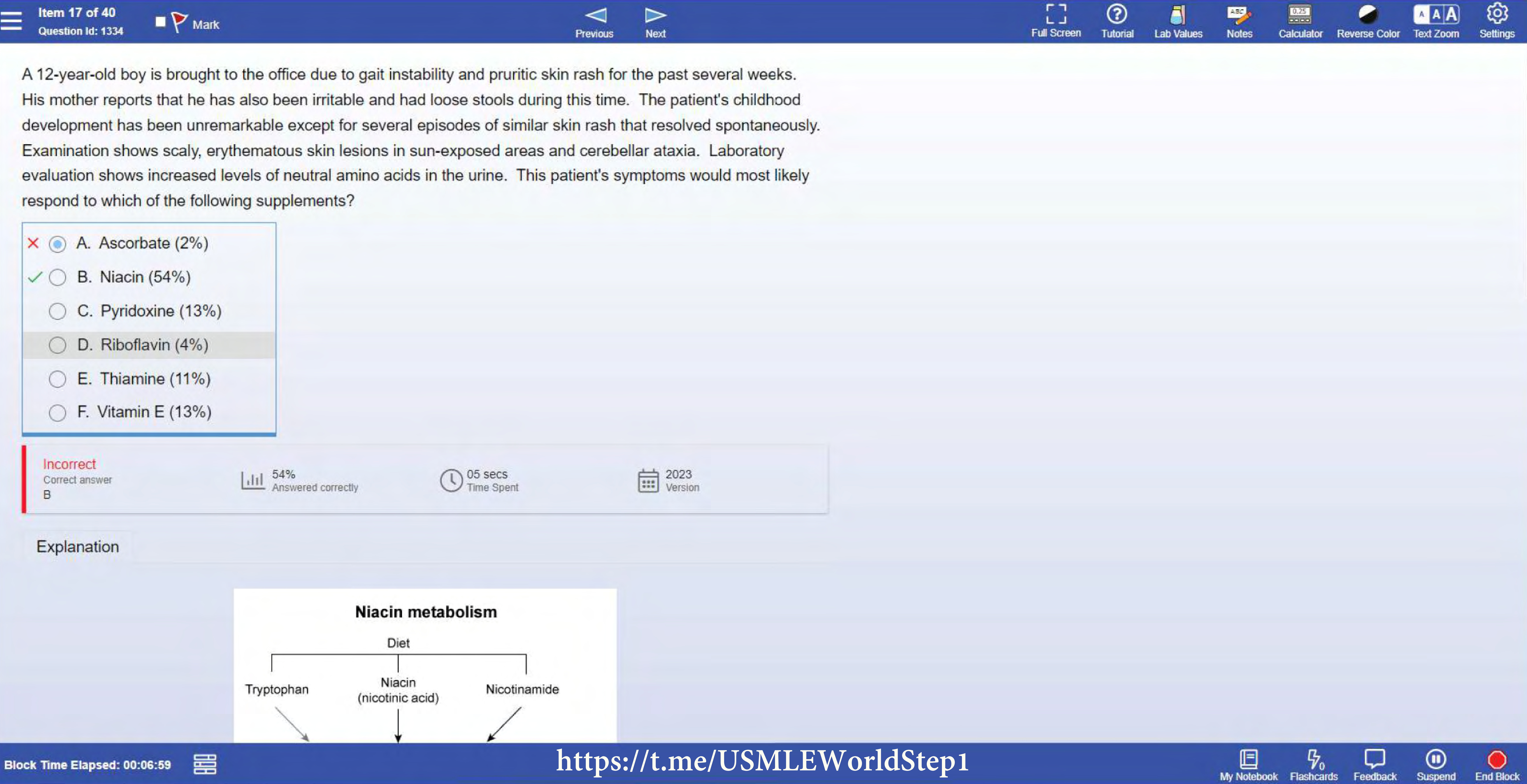
Item 17 of 40
Question Id: 1334
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 12-year-old boy is brought to the office due to gait instability and pruritic skin rash for the past several weeks. His mother reports that he has also been irritable and had loose stools during this time. The patient's childhood development has been unremarkable except for several episodes of similar skin rash that resolved spontaneously. Examination shows scaly, erythematous skin lesions in sun-exposed areas and cerebellar ataxia. Laboratory evaluation shows increased levels of neutral amino acids in the urine. This patient's symptoms would most likely respond to which of the following supplements?

- ✗ ● A. Ascorbate (2%)
- ✓ ○ B. Niacin (54%)
- ○ C. Pyridoxine (13%)
- ○ D. Riboflavin (4%)
- ○ E. Thiamine (11%)
- ○ F. Vitamin E (13%)

Incorrect
Correct answer
B

54%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

Niacin metabolism

Diet
Tryptophan
Niacin
(nicotinic acid)
Nicotinamide

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My Notebook
Flashcards
Feedback
Suspend
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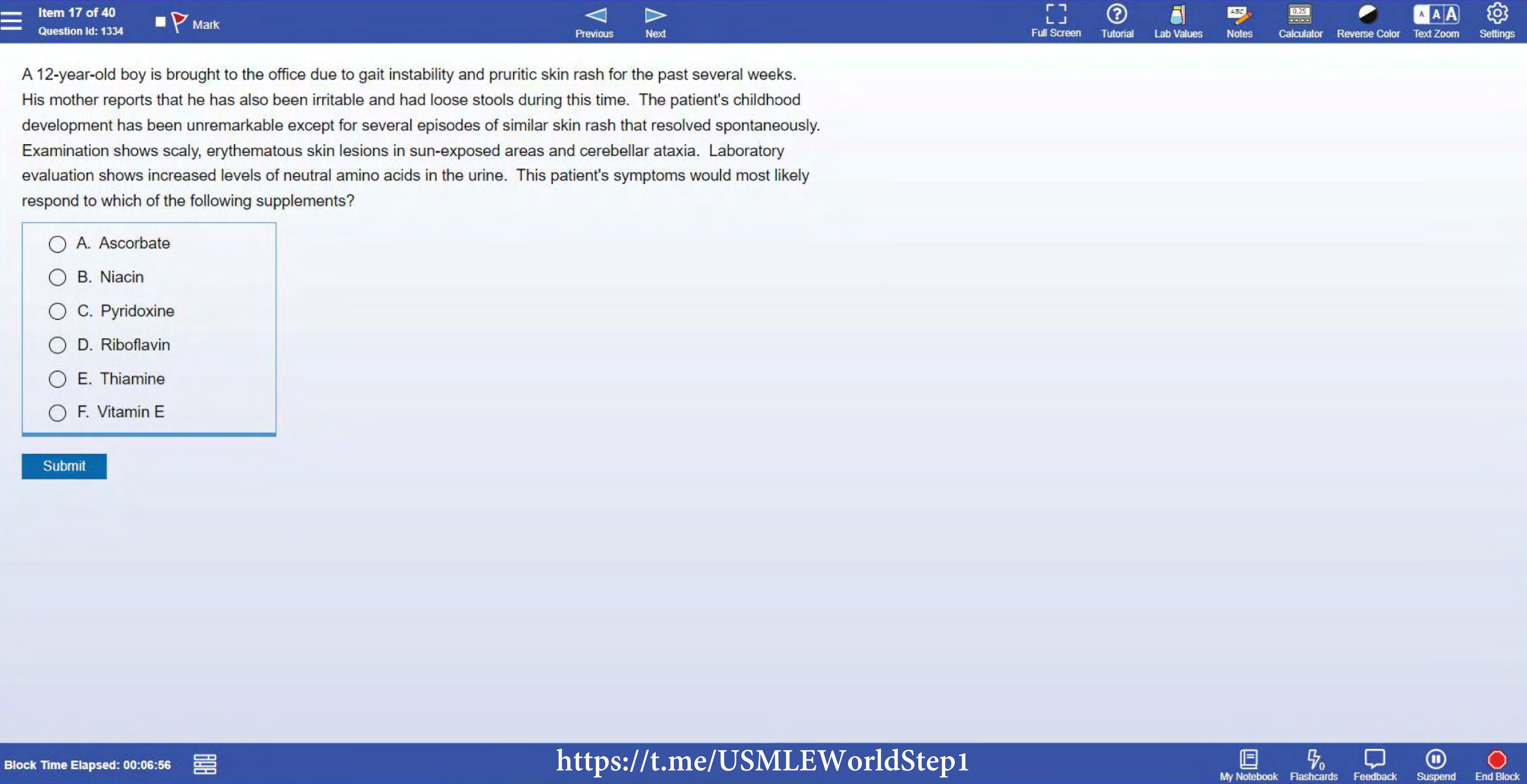
Item 17 of 40
Question Id: 1334
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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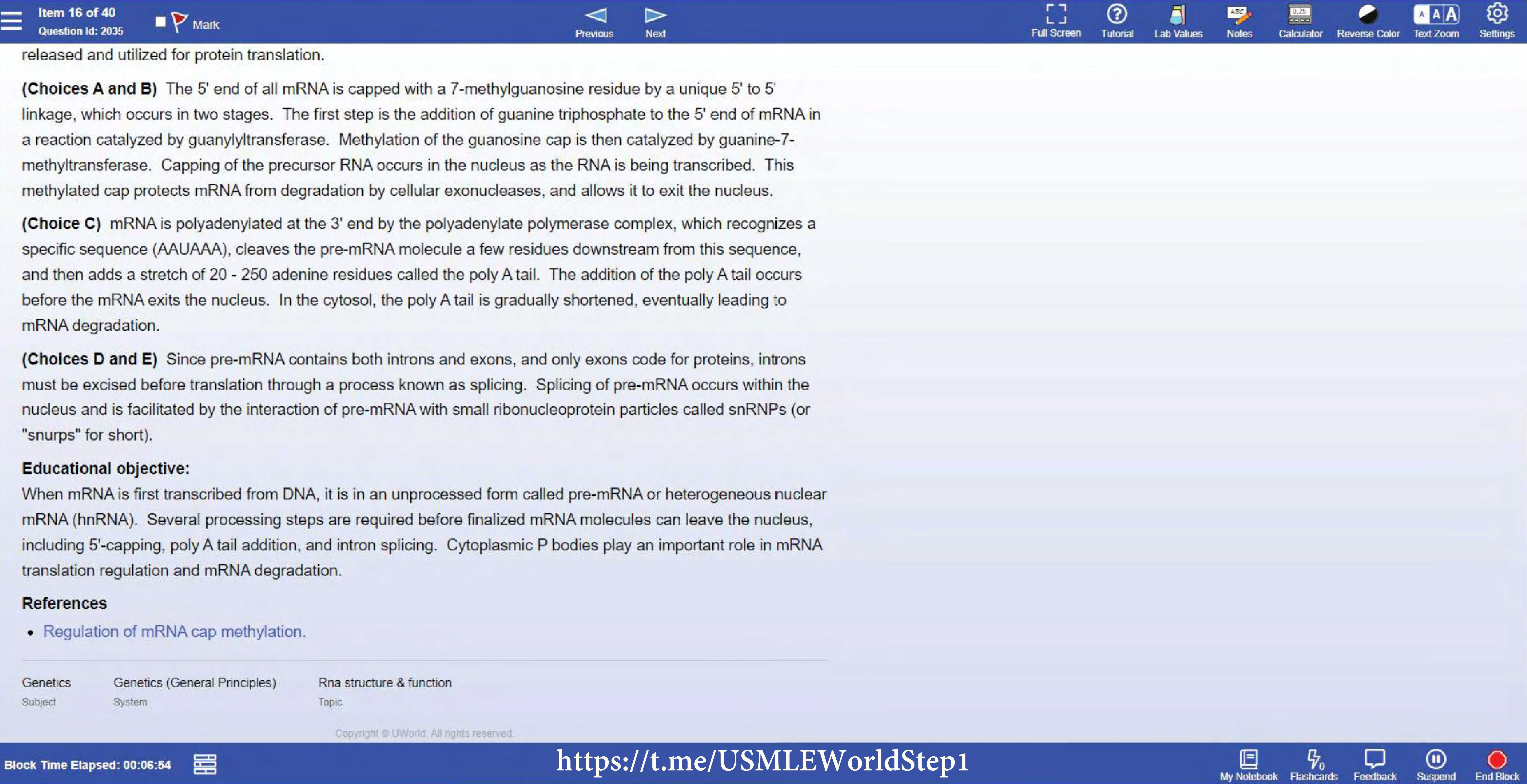
Block Time Elapsed: 00:06:56
My Notebook
Flashcards
Feedback
Suspend
End Block



released and utilized for protein translation.

(Choices A and B) The 5' end of all mRNA is capped with a 7-methylguanosine residue by a unique 5' to 5' linkage, which occurs in two stages. The first step is the addition of guanine triphosphate to the 5' end of mRNA in a reaction catalyzed by guanylyltransferase. Methylation of the guanosine cap is then catalyzed by guanine-7-methyltransferase. Capping of the precursor RNA occurs in the nucleus as the RNA is being transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it to exit the nucleus.

(Choice C) mRNA is polyadenylated at the 3' end by the polyadenylate polymerase complex, which recognizes a specific sequence (AAUAAA), cleaves the pre-mRNA molecule a few residues downstream from this sequence, and then adds a stretch of 20 - 250 adenine residues called the poly A tail. The addition of the poly A tail occurs before the mRNA exits the nucleus. In the cytosol, the poly A tail is gradually shortened, eventually leading to mRNA degradation.

(Choices D and E) Since pre-mRNA contains both introns and exons, and only exons code for proteins, introns must be excised before translation through a process known as splicing. Splicing of pre-mRNA occurs within the nucleus and is facilitated by the interaction of pre-mRNA with small ribonucleoprotein particles called snRNPs (or "snurps" for short).

Educational objective:

When mRNA is first transcribed from DNA, it is in an unprocessed form called pre-mRNA or heterogeneous nuclear mRNA (hnRNA). Several processing steps are required before finalized mRNA molecules can leave the nucleus, including 5'-capping, poly A tail addition, and intron splicing. Cytoplasmic P bodies play an important role in mRNA translation regulation and mRNA degradation.

References

- Regulation of mRNA cap methylation.

Genetics	Genetics (General Principles)	Rna structure & function
Subject	System	Topic

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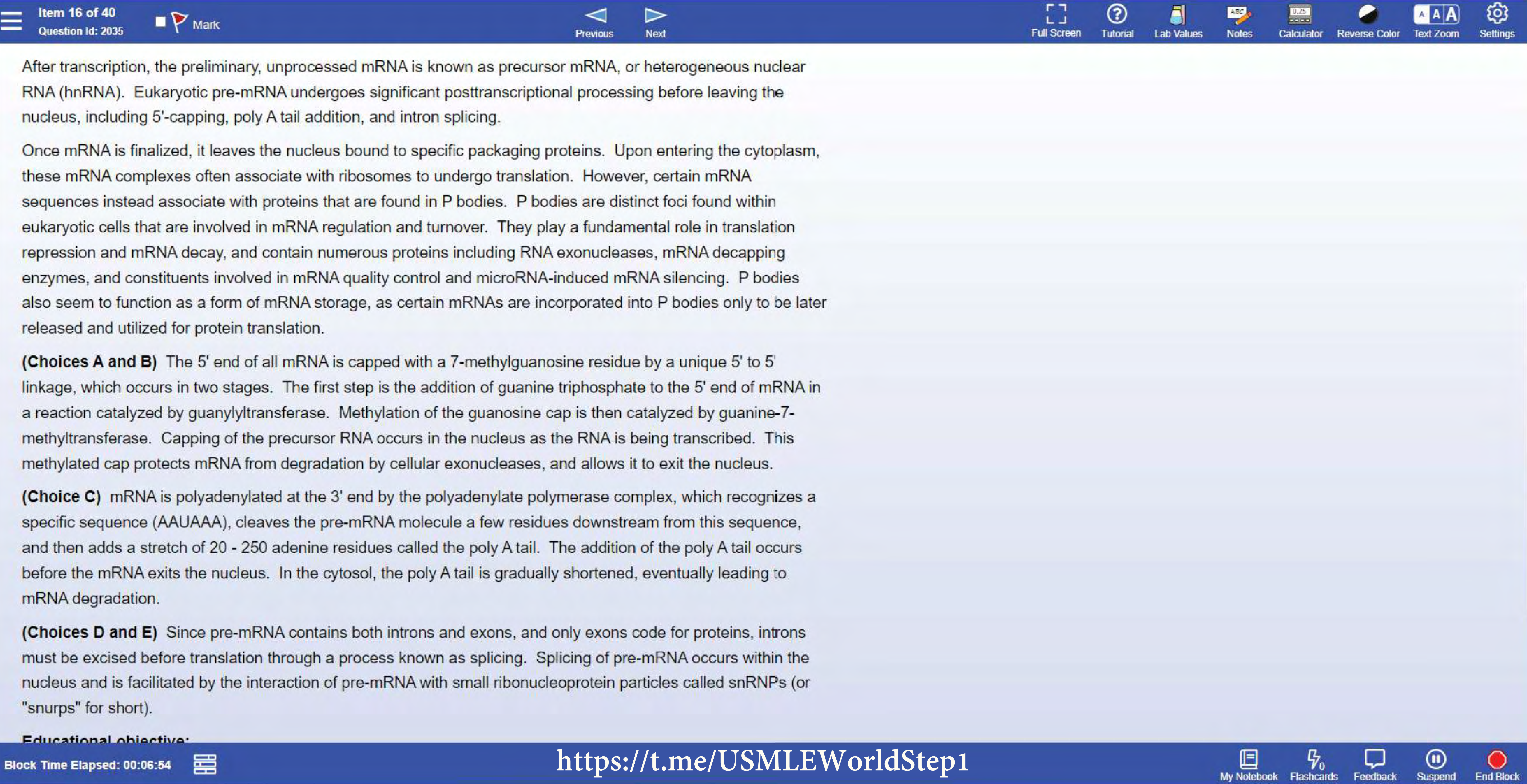

After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often associate with ribosomes to undergo translation. However, certain mRNA sequences instead associate with proteins that are found in P bodies. P bodies are distinct foci found within eukaryotic cells that are involved in mRNA regulation and turnover. They play a fundamental role in translation repression and mRNA decay, and contain numerous proteins including RNA exonucleases, mRNA decapping enzymes, and constituents involved in mRNA quality control and microRNA-induced mRNA silencing. P bodies also seem to function as a form of mRNA storage, as certain mRNAs are incorporated into P bodies only to be later released and utilized for protein translation.

(Choices A and B) The 5' end of all mRNA is capped with a 7-methylguanosine residue by a unique 5' to 5' linkage, which occurs in two stages. The first step is the addition of guanine triphosphate to the 5' end of mRNA in a reaction catalyzed by guanylyltransferase. Methylation of the guanosine cap is then catalyzed by guanine-7-methyltransferase. Capping of the precursor RNA occurs in the nucleus as the RNA is being transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it to exit the nucleus.

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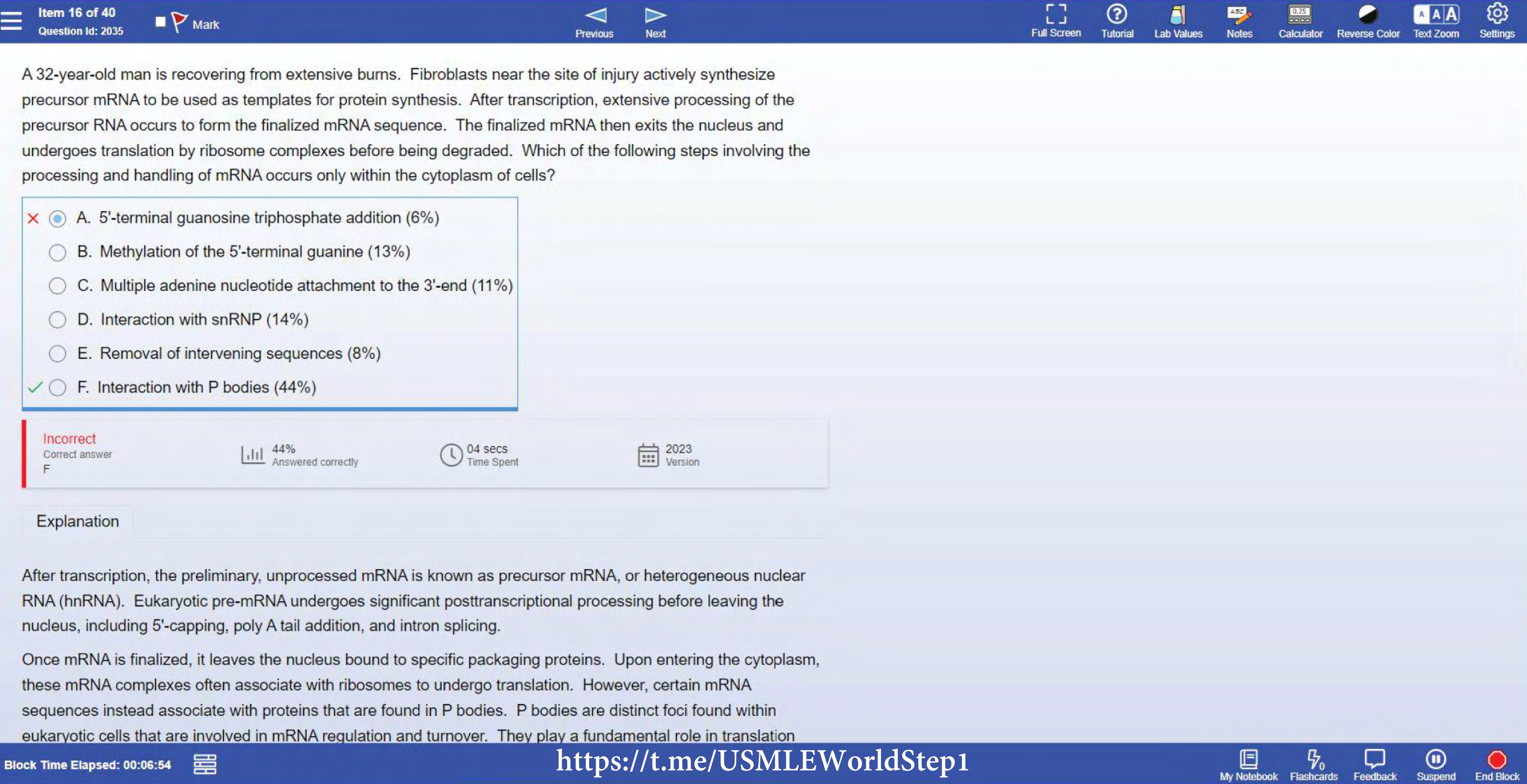
Educational objective:


Item 16 of 40
Question Id: 2035
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 32-year-old man is recovering from extensive burns. Fibroblasts near the site of injury actively synthesize precursor mRNA to be used as templates for protein synthesis. After transcription, extensive processing of the precursor RNA occurs to form the finalized mRNA sequence. The finalized mRNA then exits the nucleus and undergoes translation by ribosome complexes before being degraded. Which of the following steps involving the processing and handling of mRNA occurs only within the cytoplasm of cells?

✗ ● A. 5'-terminal guanosine triphosphate addition (6%)
○ B. Methylation of the 5'-terminal guanine (13%)
○ C. Multiple adenine nucleotide attachment to the 3'-end (11%)
○ D. Interaction with snRNP (14%)
○ E. Removal of intervening sequences (8%)
✓ ○ F. Interaction with P bodies (44%)

Incorrect
Correct answer
F

44%
Answered correctly

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Time Spent

2023
Version

Explanation

After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

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Flashcards
Feedback
Suspend
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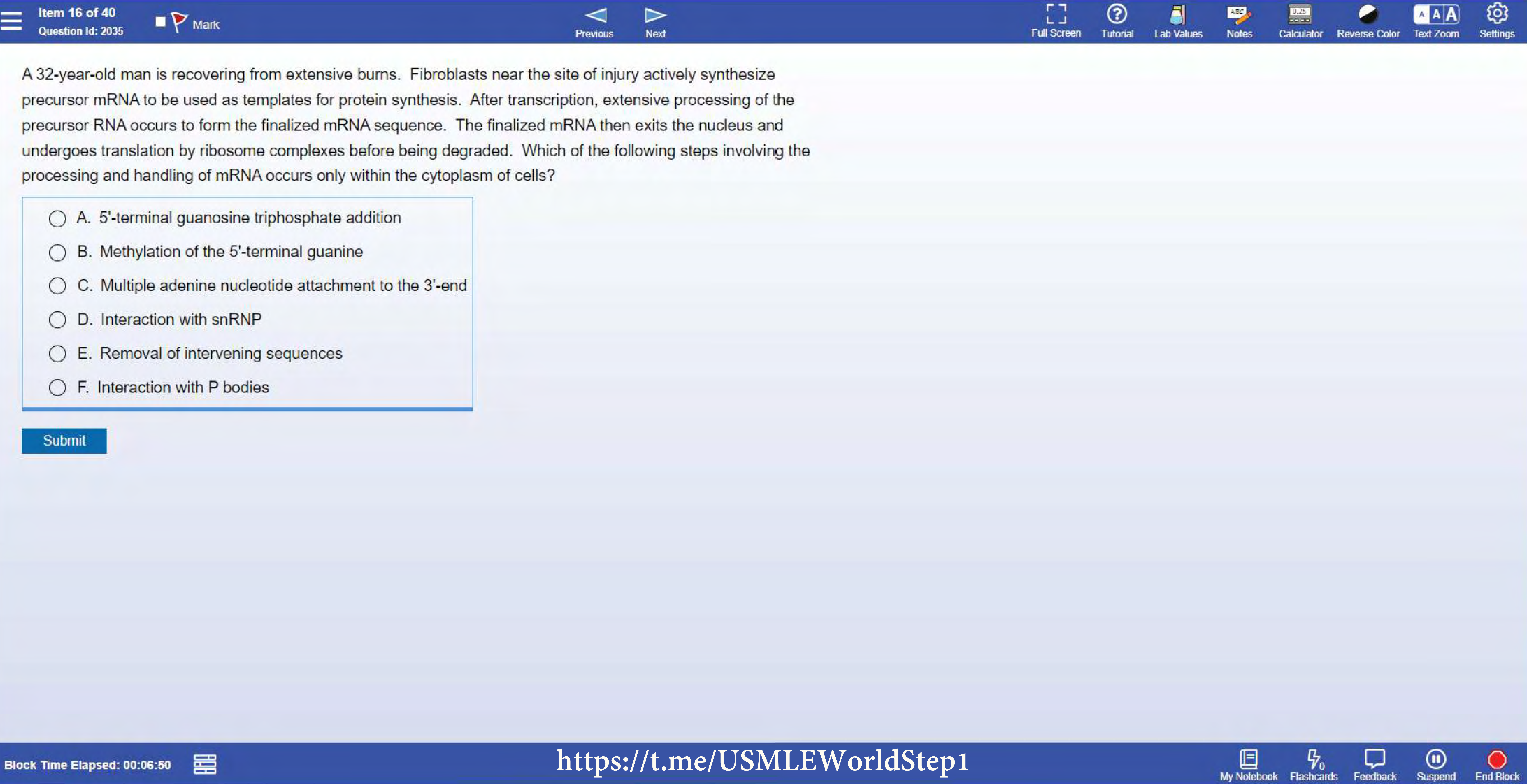
Item 16 of 40
Question Id: 2035
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ E. Removal of intervening sequences
○ F. Interaction with P bodies

Submit
Block Time Elapsed: 00:06:50
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 15 of 40
Question Id: 2044
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

Southwestern blots are used to identify and isolate proteins that bind DNA. In this technique, the target protein binds to a labeled, double-stranded DNA probe that is homologous to the protein's regulatory sequence. Of the molecules listed, c-Jun is the only DNA-binding protein. c-Jun and c-Fos are nuclear transcription factors that directly bind DNA via a leucine zipper motif. The genes that code for c-Jun and c-Fos are proto-oncogenes, genes that can become oncogenes following a mutation or with constitutive expression.

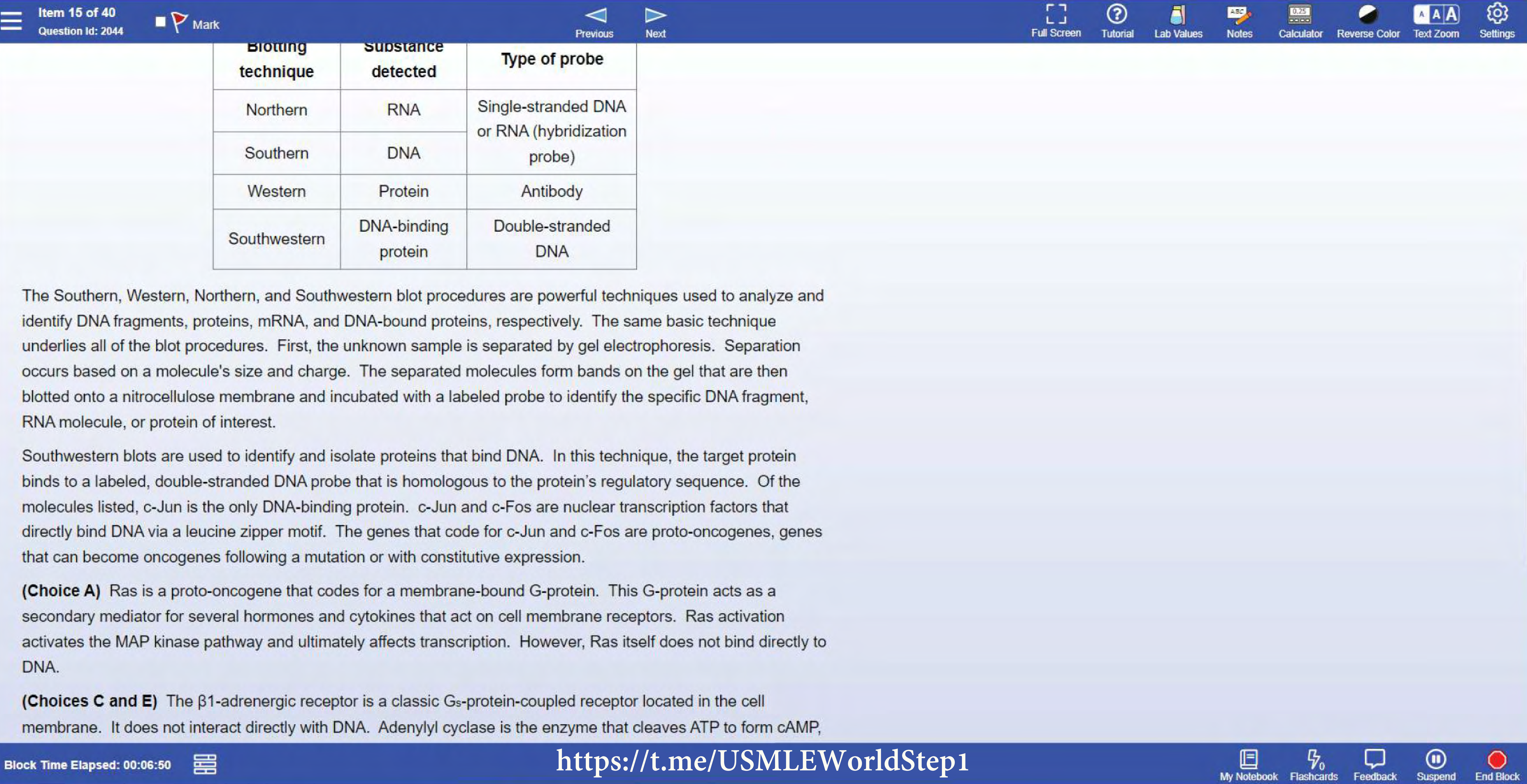
(Choice A) Ras is a proto-oncogene that codes for a membrane-bound G-protein. This G-protein acts as a secondary mediator for several hormones and cytokines that act on cell membrane receptors. Ras activation activates the MAP kinase pathway and ultimately affects transcription. However, Ras itself does not bind directly to DNA.

(Choices C and E) The β1-adrenergic receptor is a classic G_s-protein-coupled receptor located in the cell membrane. It does not interact directly with DNA. Adenylyl cyclase is the enzyme that cleaves ATP to form cAMP, the second messenger associated with G_s-protein-coupled receptors. cAMP activates protein kinase A for further downstream signaling.

(Choice D) S-100 proteins are homodimeric calcium-binding proteins, similar in structure to calmodulin and important in intracellular functions such as protein phosphorylation and cell growth and differentiation. S-100 is a marker for cells of neural crest derivation (melanocytes and Schwann cells), as well as Langerhans cells and other dendritic cells.

Educational objective:

Southwestern blotting is used to detect DNA-binding proteins such as transcription factors, nucleases, and histones.


Item 15 of 40
Question Id: 2044
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	
Western	Protein	Antibody
Southwestern	DNA-binding protein	Double-stranded DNA

The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

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(Choices C and E) The β1-adrenergic receptor is a classic G_s-protein-coupled receptor located in the cell membrane. It does not interact directly with DNA. Adenylyl cyclase is the enzyme that cleaves ATP to form cAMP,

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My Notebook
Flashcards
Feedback
Suspend
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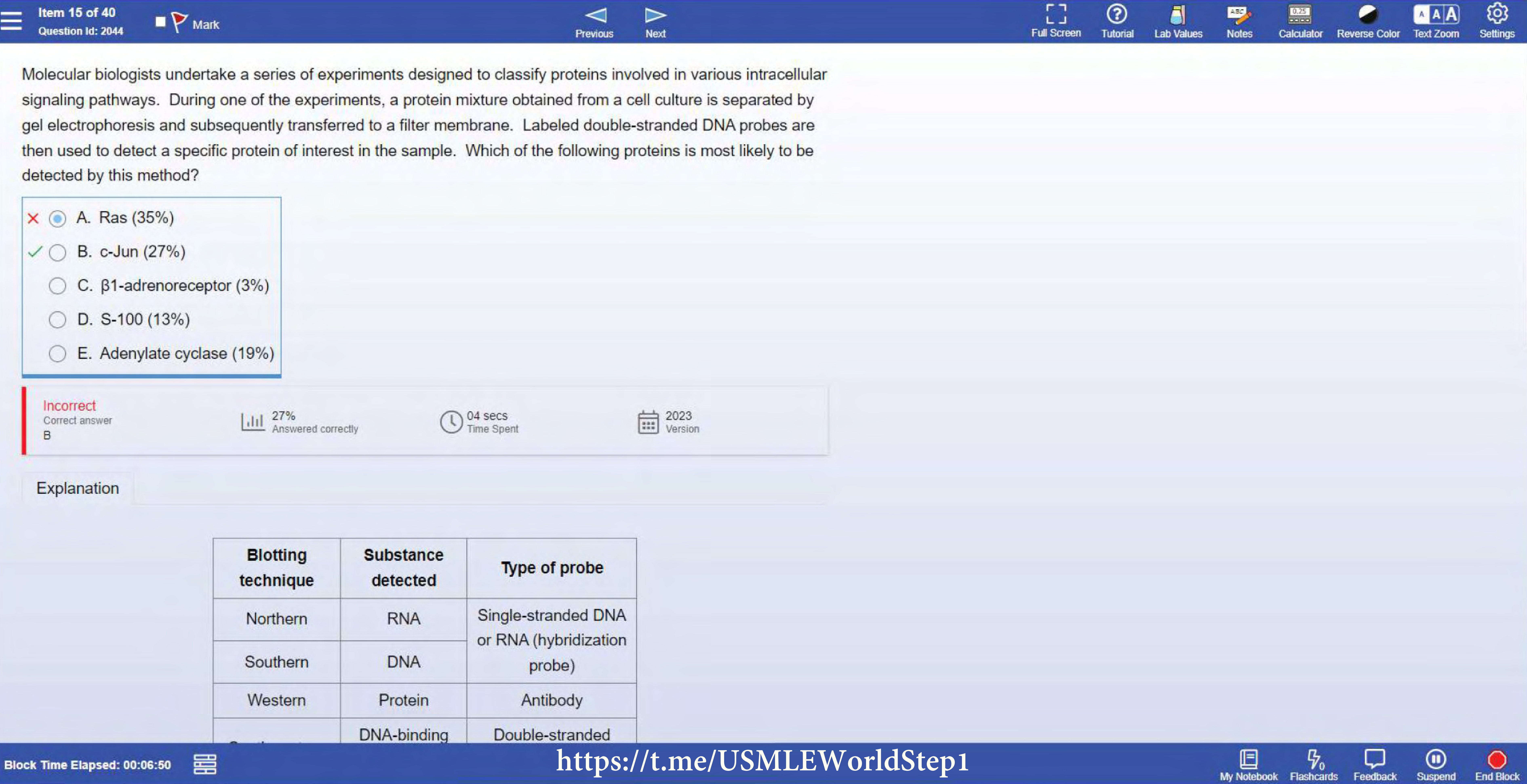
Item 15 of 40
Question Id: 2044
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:06:50
My Notebook
Flashcards
Feedback
Suspend
End Block

Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

- ✗ ● A. Ras (35%)
- ✓ ○ B. c-Jun (27%)
- ○ C. β1-adrenoreceptor (3%)
- ○ D. S-100 (13%)
- ○ E. Adenylate cyclase (19%)

Incorrect
Correct answer
B

27%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	
Western	Protein	Antibody
	DNA-binding	Double-stranded

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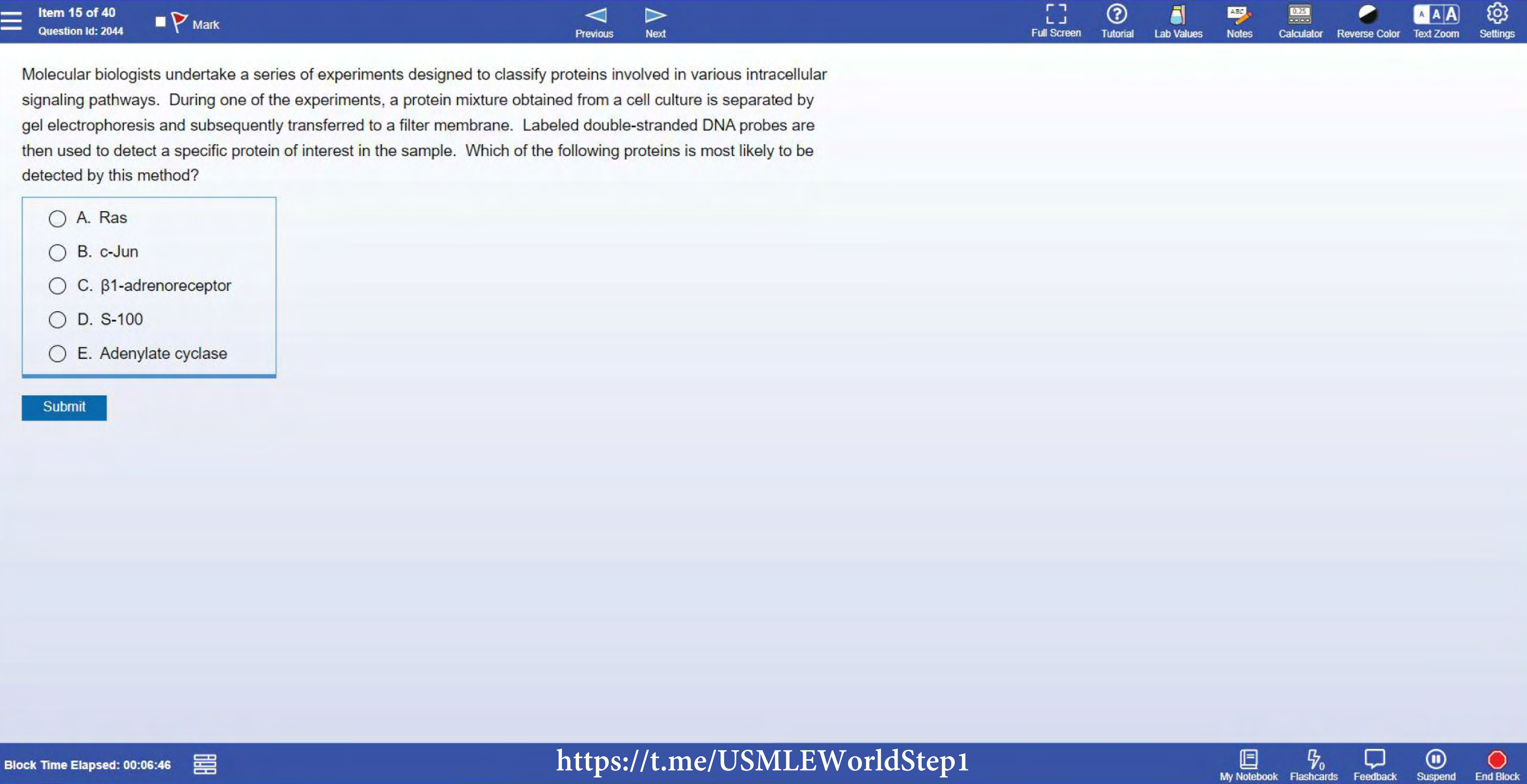
Item 15 of 40
Question Id: 2044
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:06:46
My Notebook
Flashcards
Feedback
Suspend
End Block

Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

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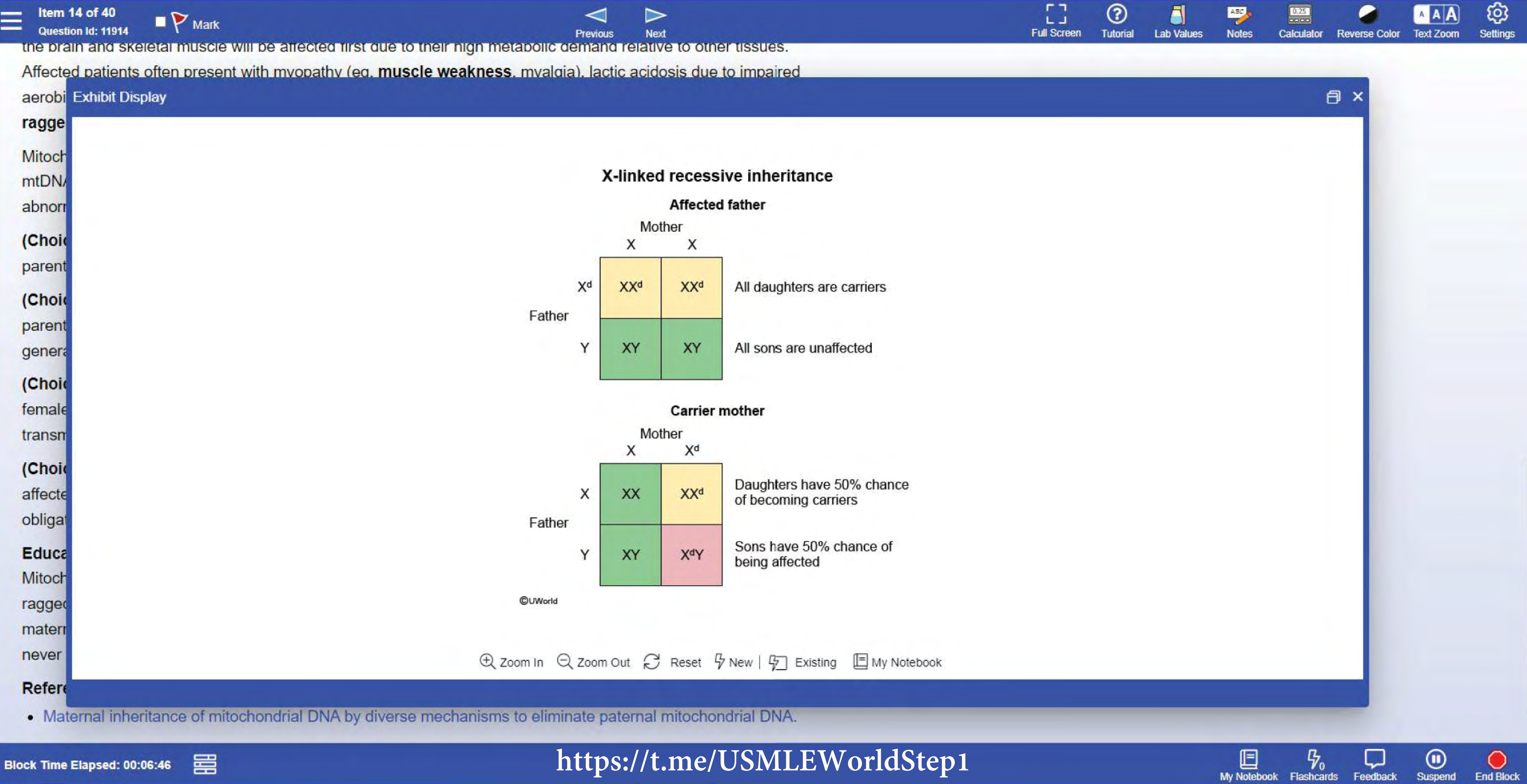
○ C. β1-adrenoreceptor
○ D. S-100
○ E. Adenylate cyclase


Item 14 of 40
Question Id: 11914
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display

the brain and skeletal muscle will be affected first due to their high metabolic demand relative to other tissues. Affected patients often present with myopathy (eg, **muscle weakness**, myalgia), lactic acidosis due to impaired

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- Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA.

X-linked recessive inheritance

Affected father

Father \ Mother	X	X	
X^d	XX^d	XX^d	All daughters are carriers
Y	XY	XY	All sons are unaffected

Carrier mother

Father \ Mother	X	X^d	
X	XX	XX^d	Daughters have 50% chance of becoming carriers
Y	XY	X^dY	Sons have 50% chance of being affected

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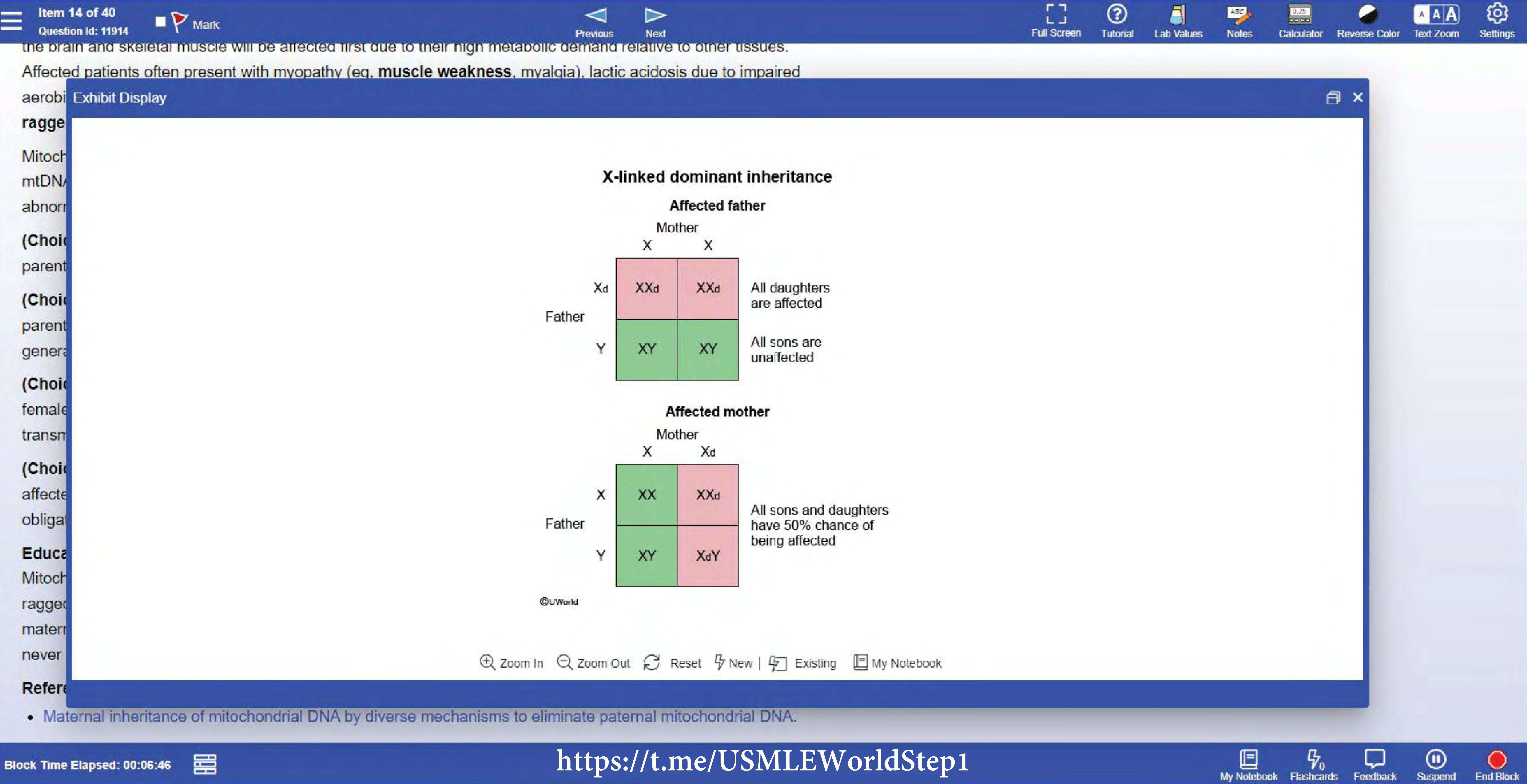
My Notebook
Block Time Elapsed: 00:06:46
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 14 of 40
Question Id: 11914
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Refer

- Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA.

Exhibit Display

X-linked dominant inheritance

Affected father

Father \ Mother	X	X	
X_d	🟥 XX_d	🟥 XX_d	All daughters are affected
Y	🟩 XY	🟩 XY	All sons are unaffected

Affected mother

Father \ Mother	X	X_d
X	🟩 XX	🟥 XX_d
Y	🟩 XY	🟥 X_dY

All sons and daughters have 50% chance of being affected

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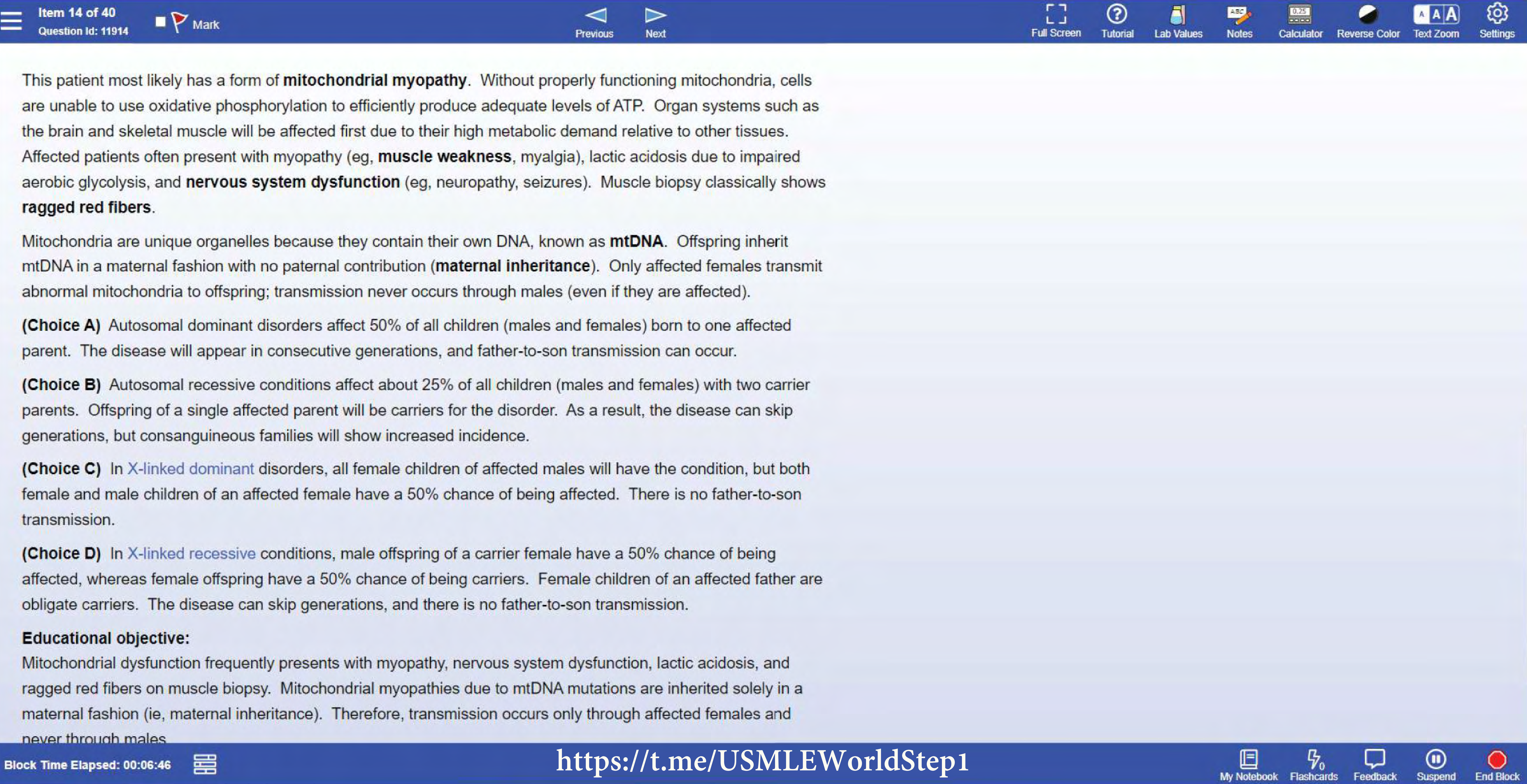
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:06:46

My Notebook
Flashcards
Feedback
Suspend
End Block



This patient most likely has a form of **mitochondrial myopathy**. Without properly functioning mitochondria, cells are unable to use oxidative phosphorylation to efficiently produce adequate levels of ATP. Organ systems such as the brain and skeletal muscle will be affected first due to their high metabolic demand relative to other tissues. Affected patients often present with myopathy (eg, **muscle weakness**, myalgia), lactic acidosis due to impaired aerobic glycolysis, and **nervous system dysfunction** (eg, neuropathy, seizures). Muscle biopsy classically shows **ragged red fibers**.

Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with no paternal contribution (**maternal inheritance**). Only affected females transmit abnormal mitochondria to offspring; transmission never occurs through males (even if they are affected).

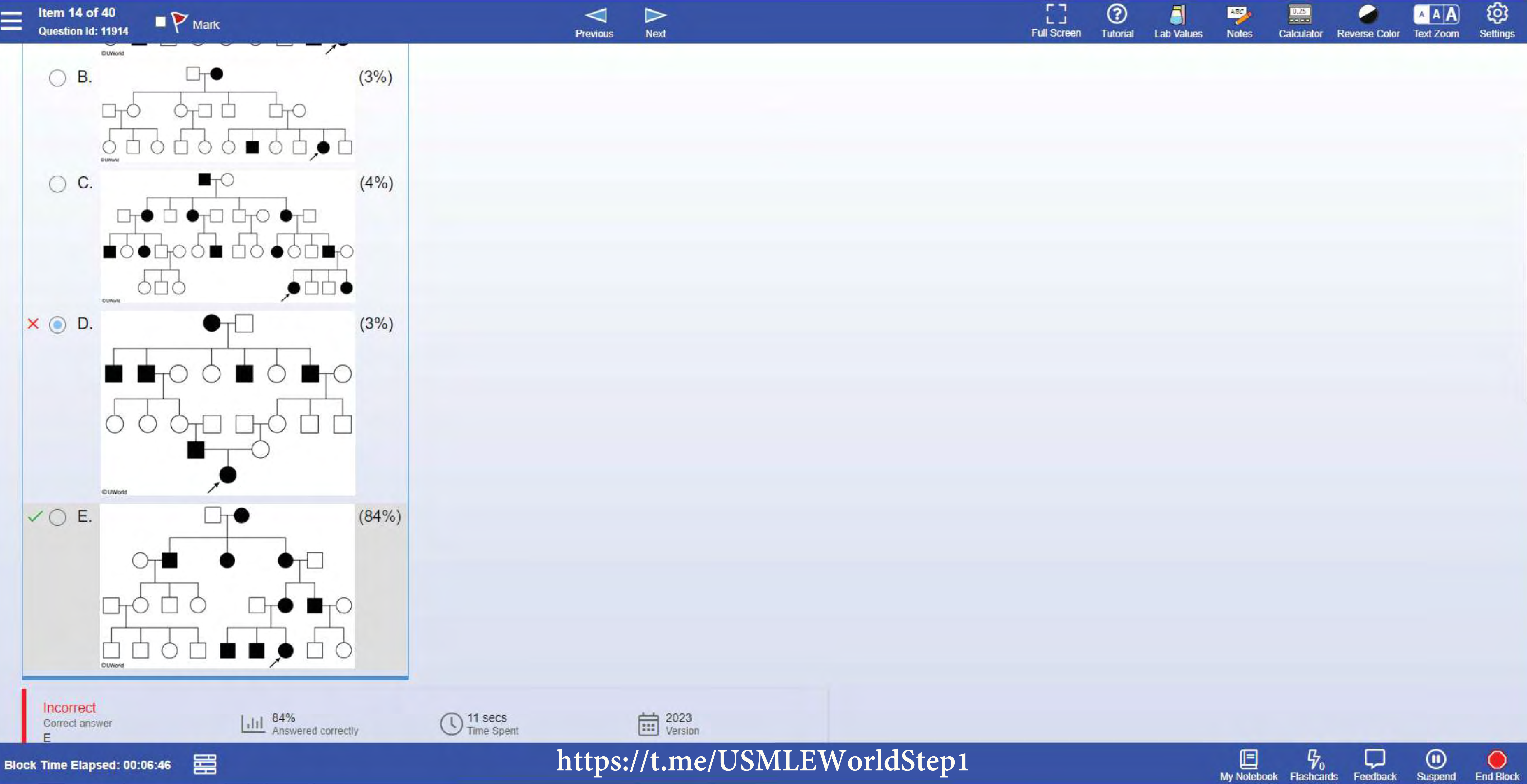
(Choice A) Autosomal dominant disorders affect 50% of all children (males and females) born to one affected parent. The disease will appear in consecutive generations, and father-to-son transmission can occur.

(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.

(Choice C) In X-linked dominant disorders, all female children of affected males will have the condition, but both female and male children of an affected female have a 50% chance of being affected. There is no father-to-son transmission.

(Choice D) In X-linked recessive conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

Educational objective:
Mitochondrial dysfunction frequently presents with myopathy, nervous system dysfunction, lactic acidosis, and ragged red fibers on muscle biopsy. Mitochondrial myopathies due to mtDNA mutations are inherited solely in a maternal fashion (ie, maternal inheritance). Therefore, transmission occurs only through affected females and never through males


Item 14 of 40
Question Id: 11914
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Block Time Elapsed: 00:06:46
My Notebook
Flashcards
Feedback
Suspend
End Block

○ B. (3%)

○ C. (4%)

✗ ● D. (3%)

✓ ○ E. (84%)

Incorrect
Correct answer
E

84% Answered correctly

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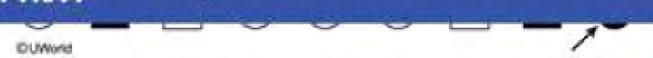
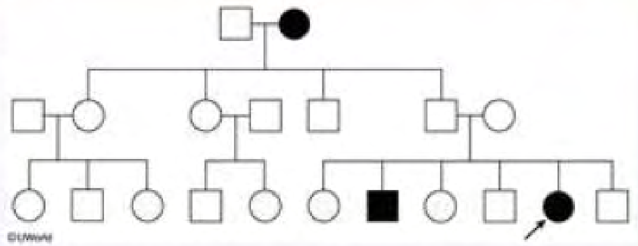
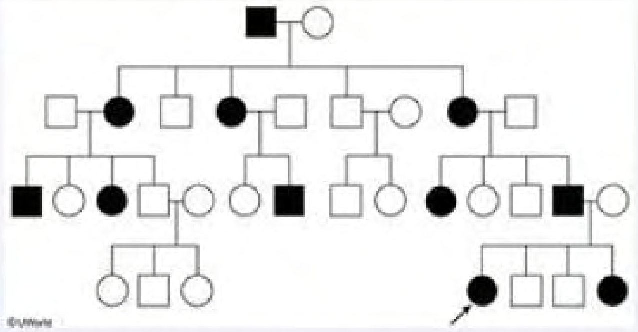


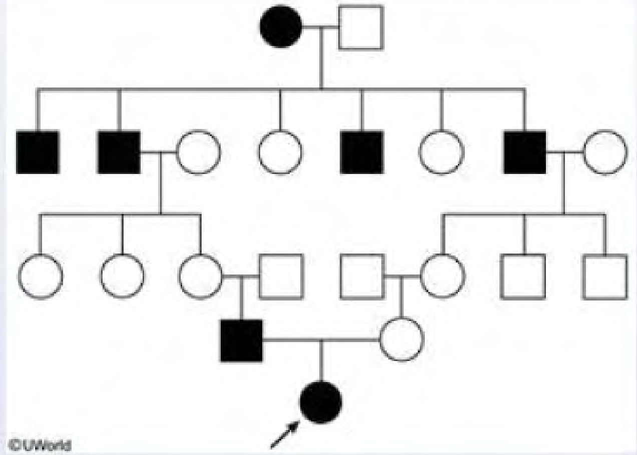
○ B.



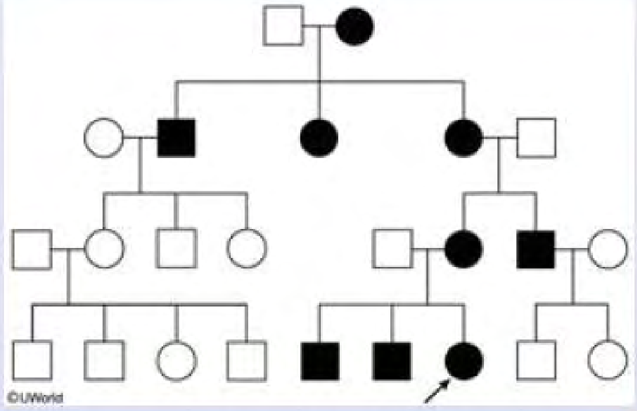
○ C.



○ D.



○ E.



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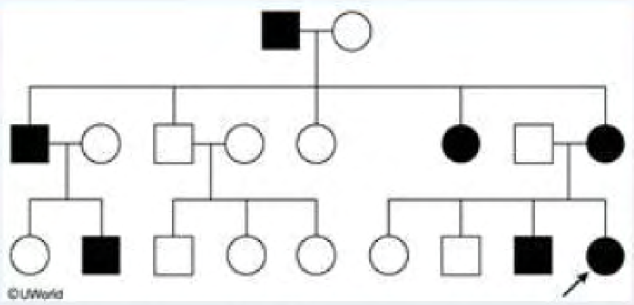
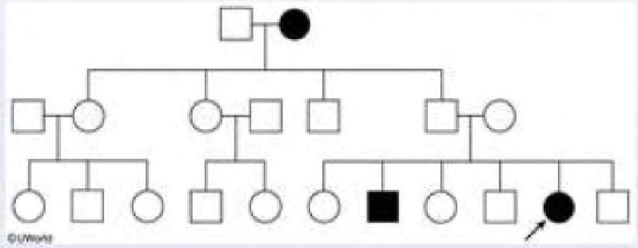
A 19-year-old woman is evaluated for new onset generalized tonic-clonic seizures. For the past several years, she has also been having erratic jerks of her arms and legs, and intermittent muscle weakness. The girl has multiple family members with similar symptoms. Neurological examination reveals decreased sensation in the lower extremities and a broad-based gait. Skeletal muscle biopsy shows ragged, red-appearing muscle fibers. Further analysis reveals that the patient's symptoms are due to a mutation affecting extranuclear DNA. Which of the following pedigrees is most likely to represent this patient's family history? (The arrow points to the patient.)

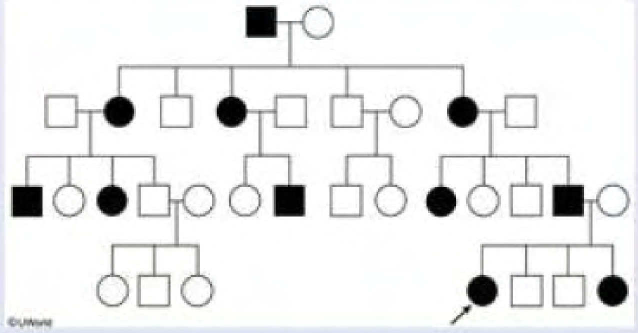
○ A.



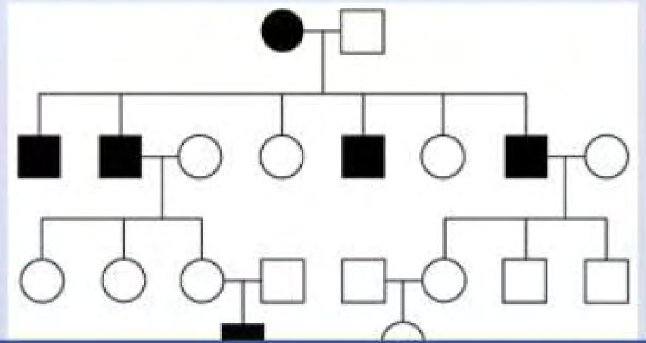
○ B.



○ C.



○ D.



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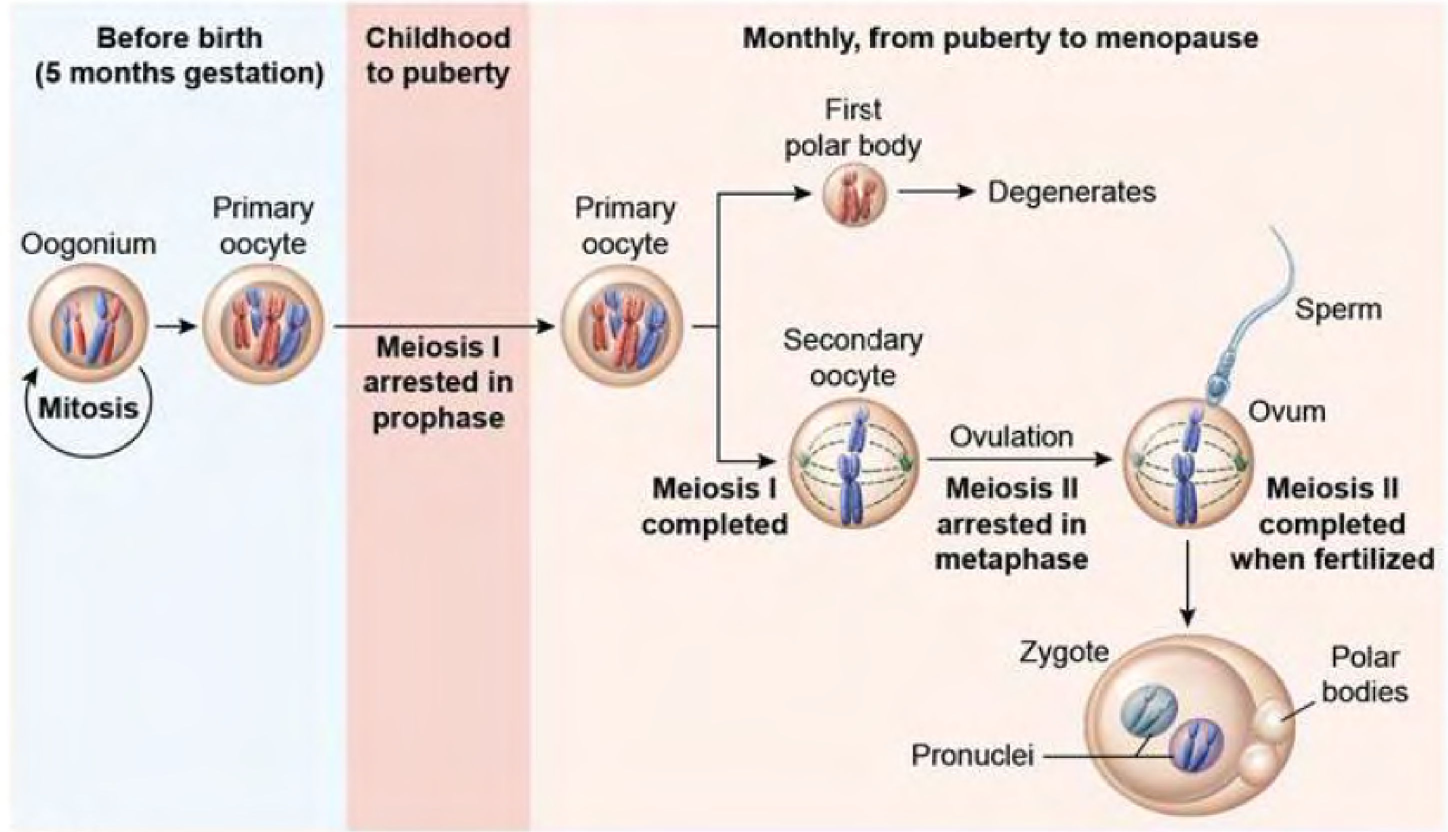
Before birth (5 months gestation)
Childhood to puberty
Monthly, from puberty to menopause
Oogonium
Mitosis
Primary oocyte
Meiosis I arrested in prophase
Primary oocyte
First polar body
Degenerates
Secondary oocyte
Meiosis I completed
Ovulation
Meiosis II arrested in metaphase
Sperm
Ovum
Meiosis II completed when fertilized
Zygote
Polar bodies
Pronuclei

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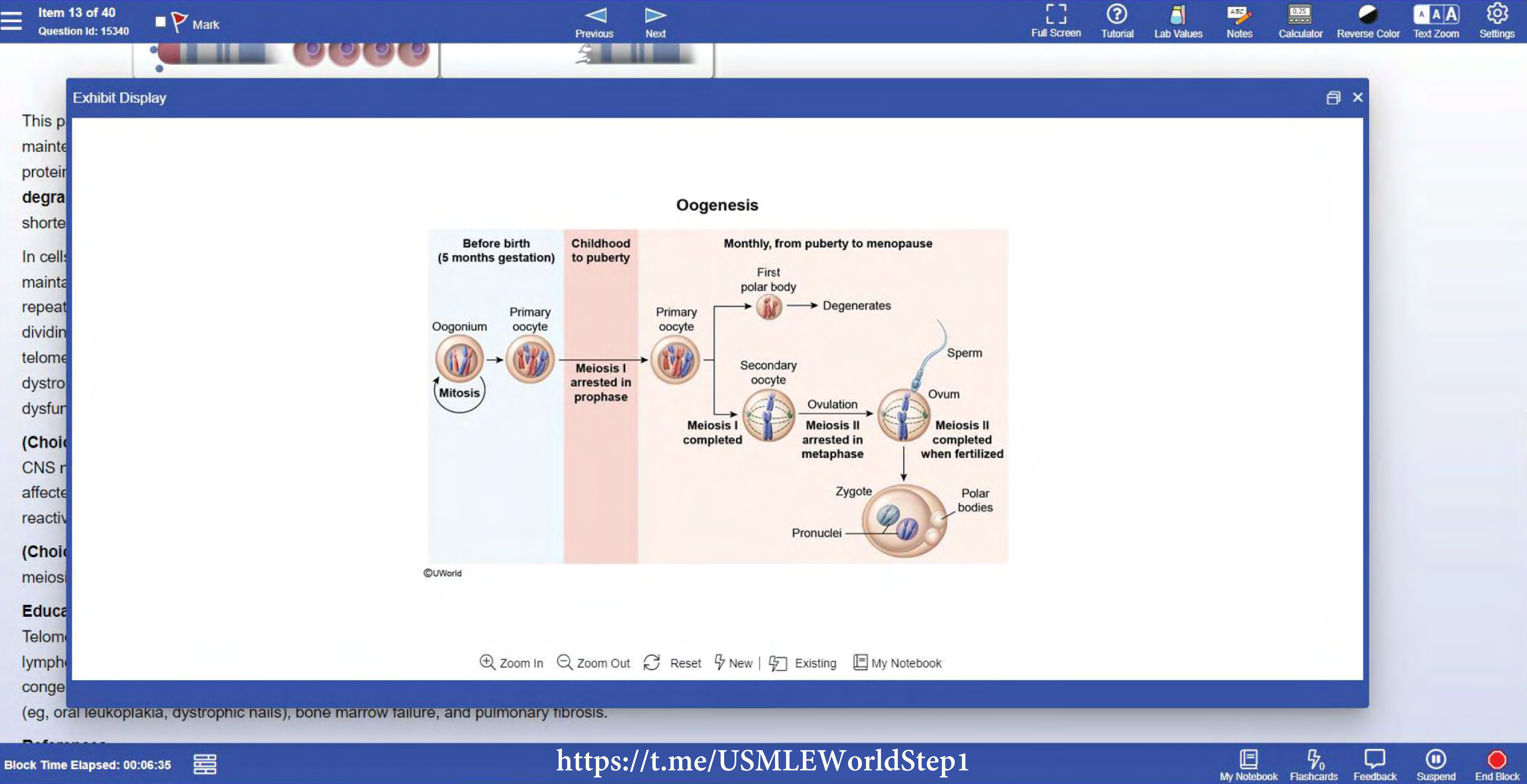
Item 13 of 40
Question Id: 15340
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Oogenesis
Before birth (5 months gestation)
Childhood to puberty
Monthly, from puberty to menopause
Oogonium
Mitosis
Primary oocyte
Meiosis I arrested in prophase
Primary oocyte
First polar body
Degenerates
Secondary oocyte
Meiosis I completed
Ovulation
Meiosis II arrested in metaphase
Sperm
Ovum
Meiosis II completed when fertilized
Zygote
Polar bodies
Pronuclei
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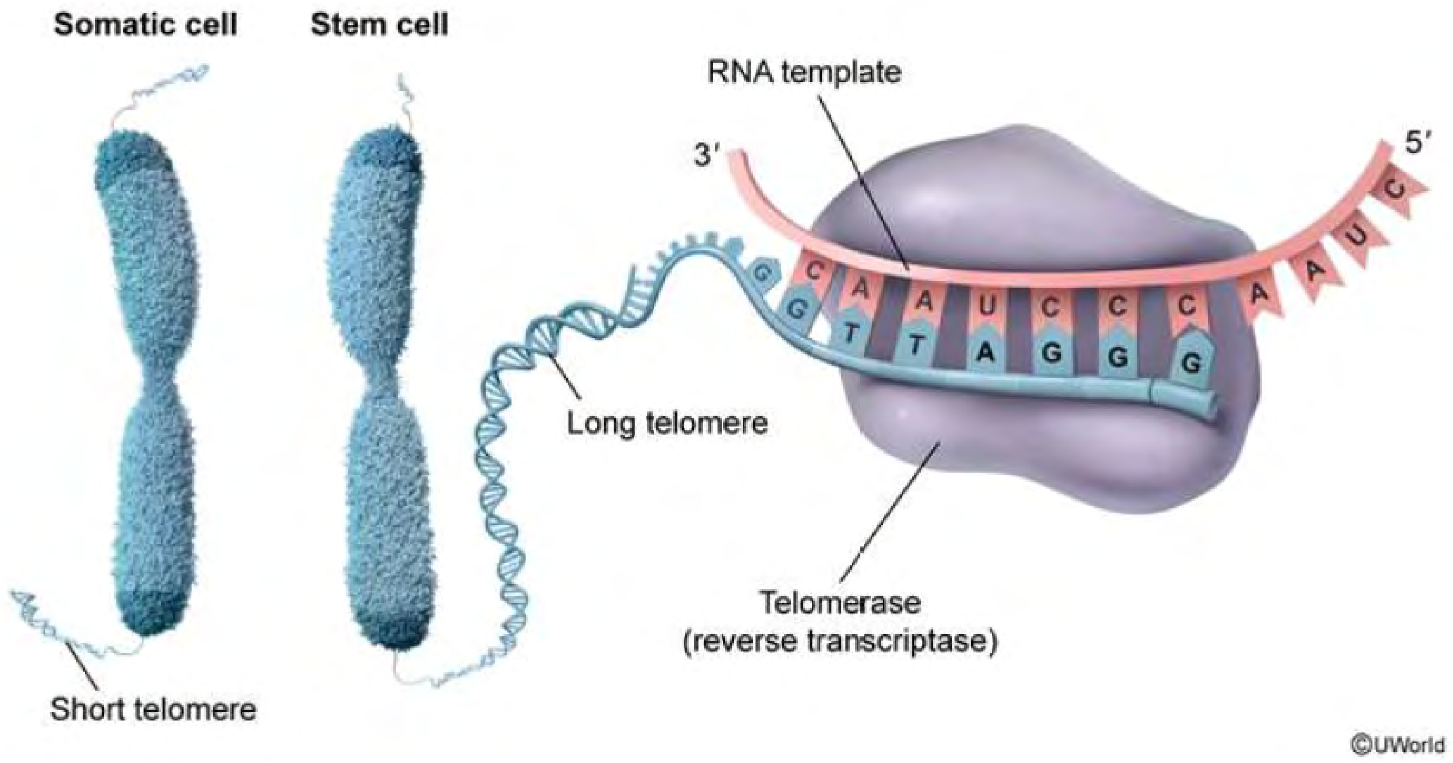
Item 13 of 40
Question Id: 15340

Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Exhibit Display



Somatic cell
Stem cell
RNA template
3′
5′
C A A U C C C A A U C
G G T T A G G G
Long telomere
Telomerase
(reverse transcriptase)
Short telomere
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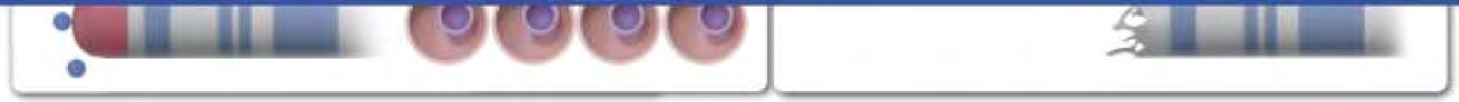

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This patient has dyskeratosis congenita; a genetic disorder involving a mutation in the genes related to telomere maintenance (eg, telomerase reverse transcriptase) that results in short telomeres. **Telomeres** are a complex of protein (eg, shelterin) and DNA repeats (eg, TTAGGG) at the ends of chromosomes that **prevent chromosomal degradation** and fusion with neighboring chromosomes. With each cellular division telomeres progressively shorten, eventually reaching a critical length at which apoptosis or senescence is triggered.

In cells with a high turnover rate (eg, epithelial cells, lymphocytes, **hematopoietic stem cells**), telomere length is maintained by telomerase. This complex, composed of an RNA template and a reverse transcriptase, adds DNA repeats to the end of telomeres as they are lost with cell division. Without normal telomerase activity, rapidly dividing cells cannot maintain chromosomal integrity, triggering **premature cell death**. In patients with short telomere disorders, loss of these cells can cause characteristic mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), **bone marrow failure** (eg, pancytopenia), and pulmonary fibrosis (due to alveolar epithelial dysfunction).

(Choices A, B, C, and F) Telomerase is inactivated in long-lived, differentiated cells such as cardiac myocytes, CNS neurons, compact bone osteocytes, and vascular endothelial cells; therefore, these cells are not likely to be affected by this patient's mutation. However, in cancer cells derived from differentiated cells, telomerase is reactivated, allowing continuous cellular division without loss of telomere length.

(Choice E) Secondary oocytes are immature ova that form as a result of the division of a primary oocyte during meiosis I. They do not continue to divide and therefore are also not likely to be affected by this patient's mutation.

Educational objective:

Telomeres help maintain chromosomal integrity and are preserved in rapidly dividing cell lines (eg, epithelial cells, lymphocytes, hematopoietic stem cells) by telomerase. Disorders involving telomerase function (eg, dyskeratosis congenita) result in premature death of cells with high turnover, characteristically causing mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), bone marrow failure, and pulmonary fibrosis.

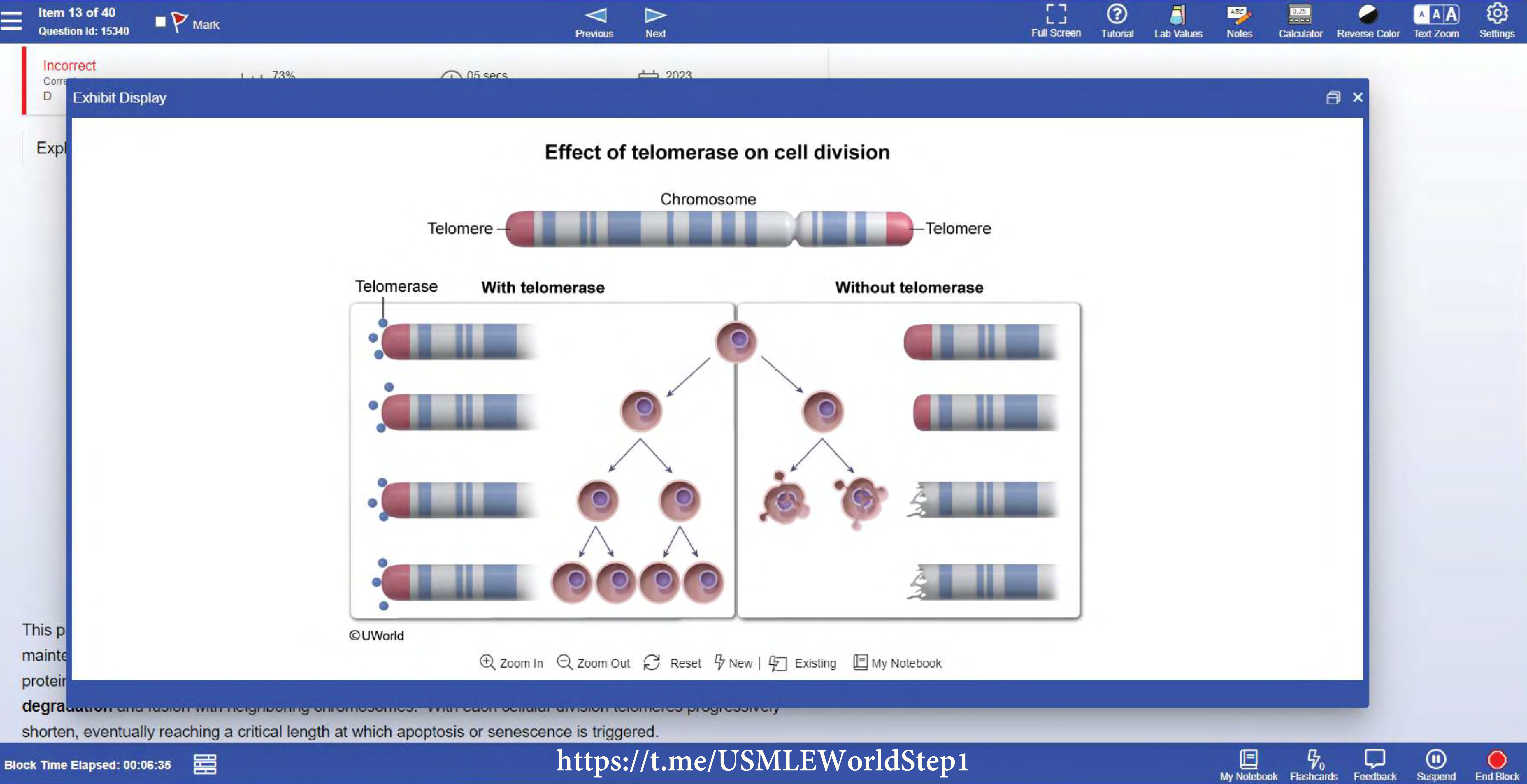
Item 13 of 40
Question Id: 15340
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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Exhibit Display
Chromosome
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My Notebook
Block Time Elapsed: 00:06:35
My Notebook
Flashcards
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Suspend
End Block

Effect of telomerase on cell division

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degra and fusion with neighboring chromosomes. With each cellular division telomeres progressively shorten, eventually reaching a critical length at which apoptosis or senescence is triggered.

An 18-year-old woman comes to the office for evaluation of graying hair. The patient has no other concerns and has otherwise been healthy. She reports that her mother had similar features at a young age and died of progressive pulmonary fibrosis. Examination shows diffuse gray hair. There are white patches on the surface of the tongue. Cardiopulmonary examination is unremarkable, and the abdomen is soft and nondistended. Skin examination shows areas of reticular hyperpigmentation on the neck and torso. The nails of the fingers and toes appear thin. Genetic testing reveals a loss-of-function mutation affecting the telomerase reverse transcriptase gene. Which of the following cell types is most likely to be affected by this mutation?

- ✗ ● A. Cardiac myocytes (1%)
- ○ B. CNS neurons (5%)
- ○ C. Compact bone osteocytes (2%)
- ✓ ○ D. Hematopoietic stem cells (73%)
- ○ E. Secondary oocytes (3%)
- ○ F. Vascular endothelial cells (13%)

Incorrect
Correct answer
D

73%
Answered correctly

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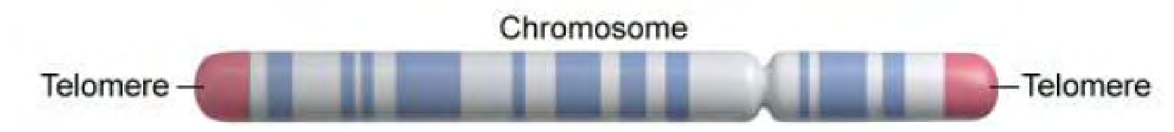
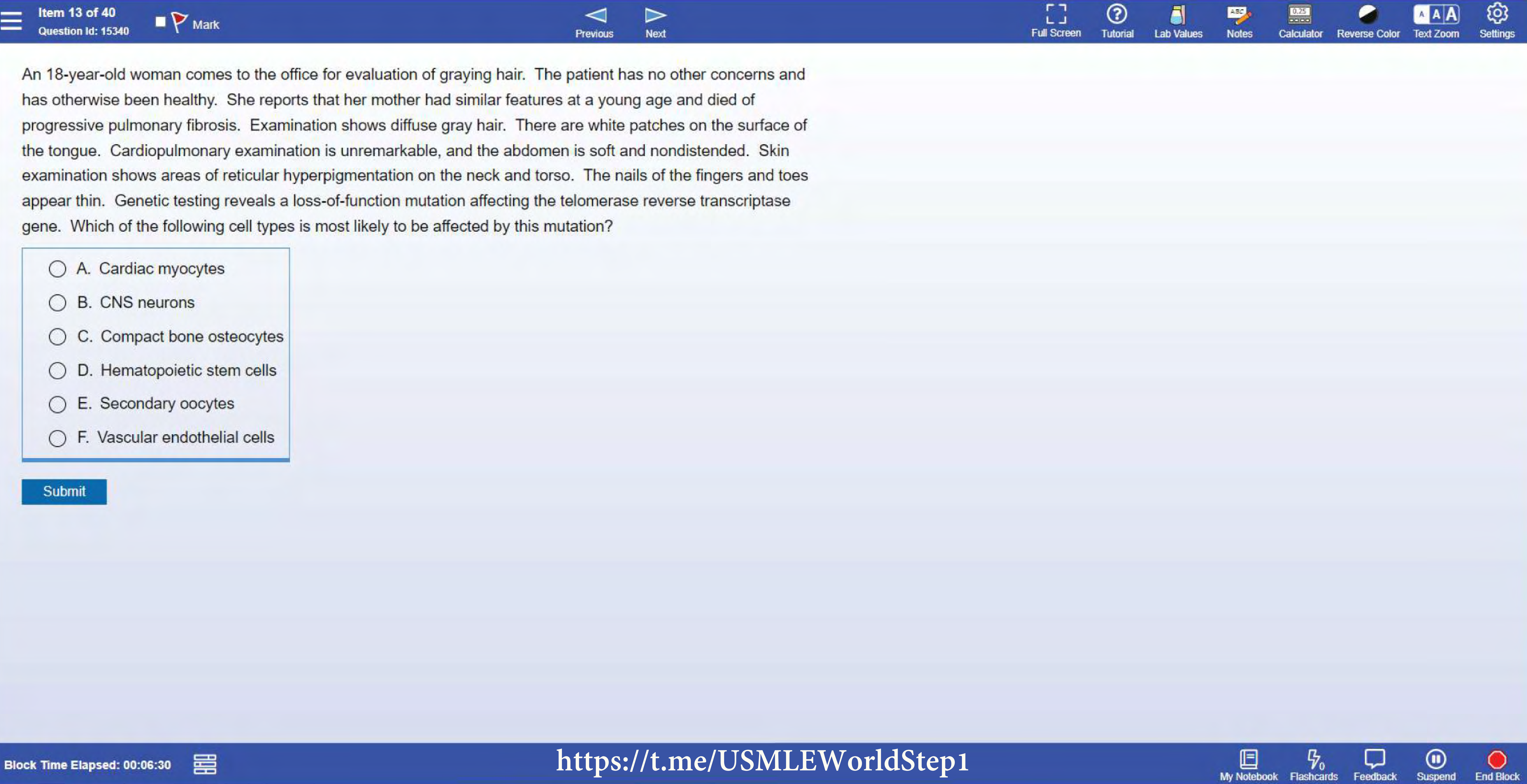
Explanation

Effect of telomerase on cell division




Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 13 of 40
Question Id: 15340

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○ A. Cardiac myocytes
○ B. CNS neurons
○ C. Compact bone osteocytes
○ D. Hematopoietic stem cells
○ E. Secondary oocytes
○ F. Vascular endothelial cells

Submit

Block Time Elapsed: 00:06:30

Item 12 of 40
Question Id: 1435

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

DNA polymerase I	- Removal of RNA primer (5′ → 3′ exonuclease activity) & replacement with DNA

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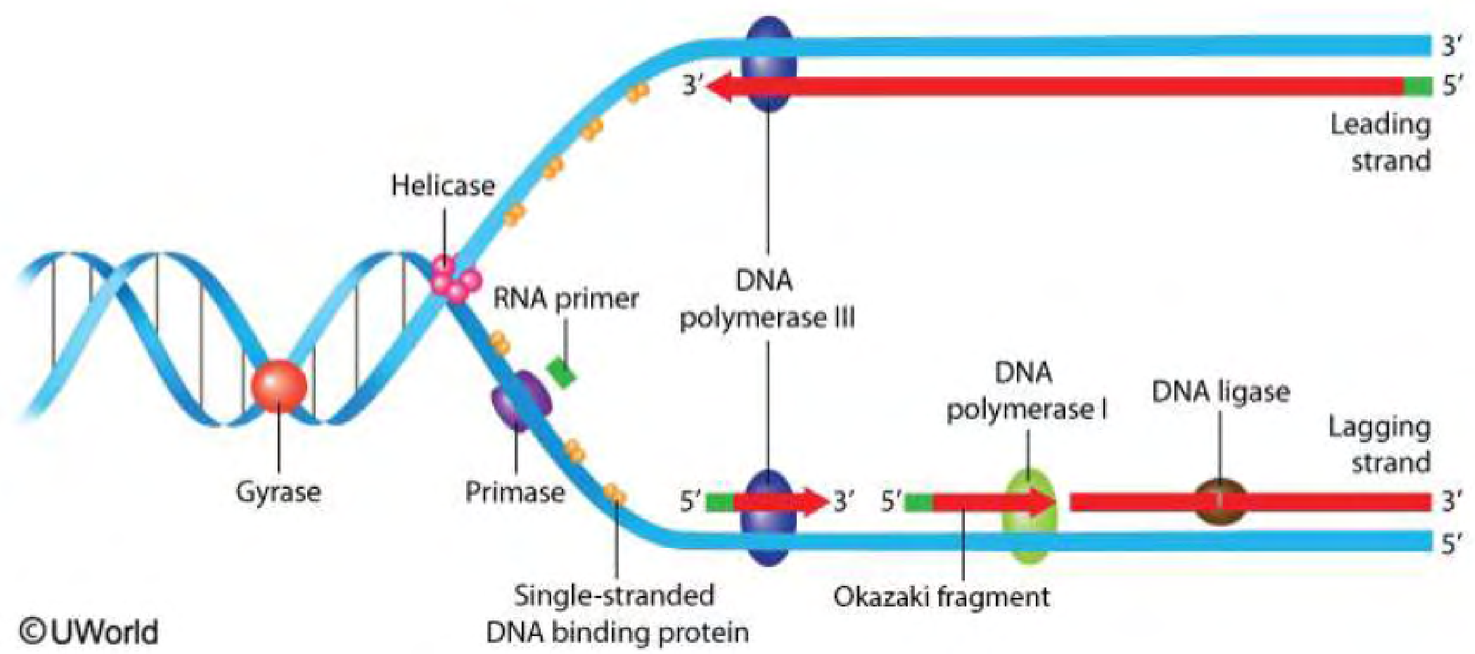
Educational objective:

Exhibit Display

Prokaryotic DNA replication fork



3′
5′
3′
Leading strand
Helicase
RNA primer
DNA polymerase III
DNA polymerase I
DNA ligase
Lagging strand
Gyrase
Primase
5′
3′
5′
3′
5′
Single-stranded DNA binding protein
Okazaki fragment

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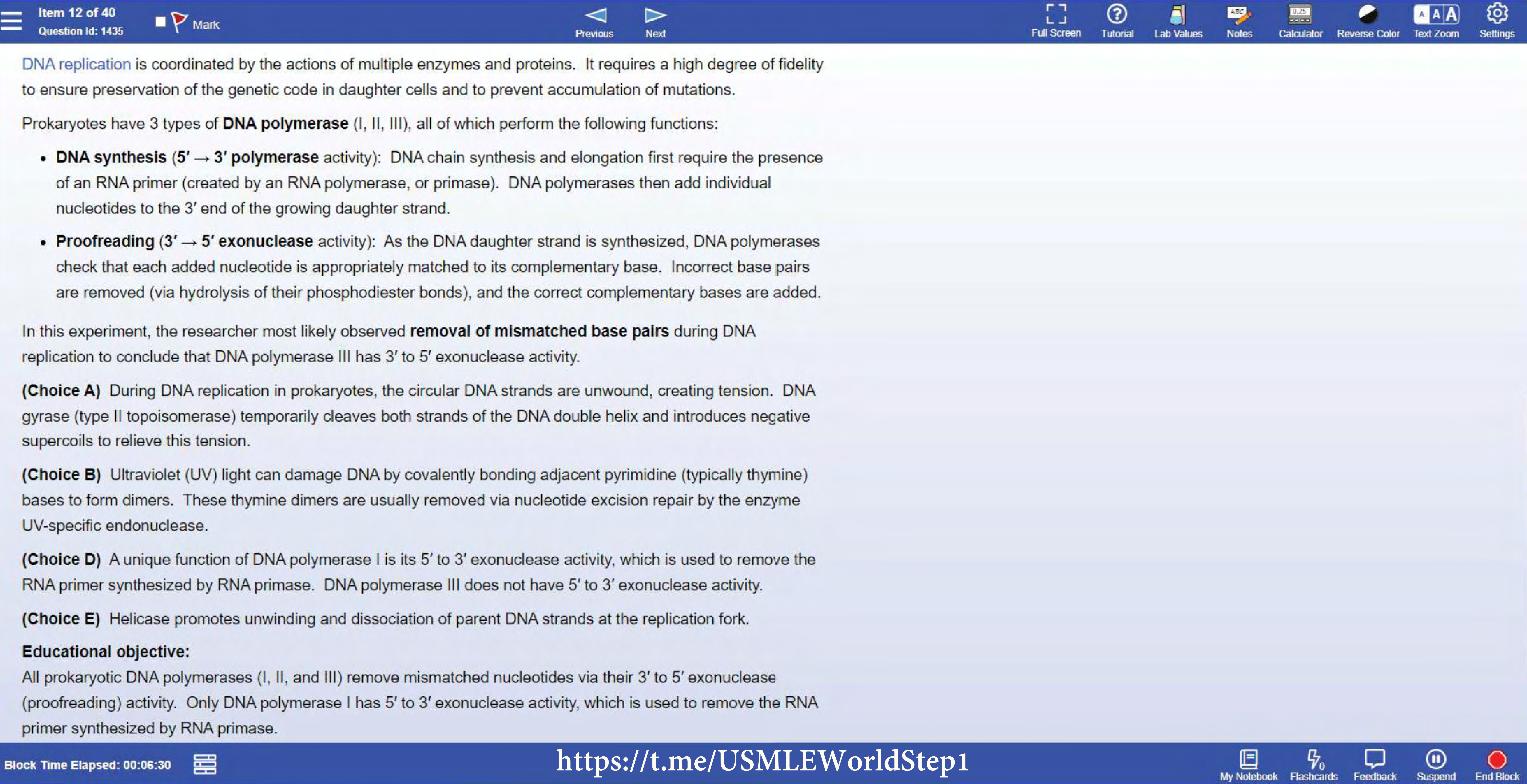

DNA replication is coordinated by the actions of multiple enzymes and proteins. It requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells and to prevent accumulation of mutations.

Prokaryotes have 3 types of **DNA polymerase** (I, II, III), all of which perform the following functions:

- **DNA synthesis** (**5′ → 3′ polymerase** activity): DNA chain synthesis and elongation first require the presence of an RNA primer (created by an RNA polymerase, or primase). DNA polymerases then add individual nucleotides to the 3′ end of the growing daughter strand.
- **Proofreading** (**3′ → 5′ exonuclease** activity): As the DNA daughter strand is synthesized, DNA polymerases check that each added nucleotide is appropriately matched to its complementary base. Incorrect base pairs are removed (via hydrolysis of their phosphodiester bonds), and the correct complementary bases are added.

In this experiment, the researcher most likely observed **removal of mismatched base pairs** during DNA replication to conclude that DNA polymerase III has 3′ to 5′ exonuclease activity.

(Choice A) During DNA replication in prokaryotes, the circular DNA strands are unwound, creating tension. DNA gyrase (type II topoisomerase) temporarily cleaves both strands of the DNA double helix and introduces negative supercoils to relieve this tension.

(Choice B) Ultraviolet (UV) light can damage DNA by covalently bonding adjacent pyrimidine (typically thymine) bases to form dimers. These thymine dimers are usually removed via nucleotide excision repair by the enzyme UV-specific endonuclease.

(Choice D) A unique function of DNA polymerase I is its 5′ to 3′ exonuclease activity, which is used to remove the RNA primer synthesized by RNA primase. DNA polymerase III does not have 5′ to 3′ exonuclease activity.

(Choice E) Helicase promotes unwinding and dissociation of parent DNA strands at the replication fork.

Educational objective:

All prokaryotic DNA polymerases (I, II, and III) remove mismatched nucleotides via their 3′ to 5′ exonuclease (proofreading) activity. Only DNA polymerase I has 5′ to 3′ exonuclease activity, which is used to remove the RNA primer synthesized by RNA primase.

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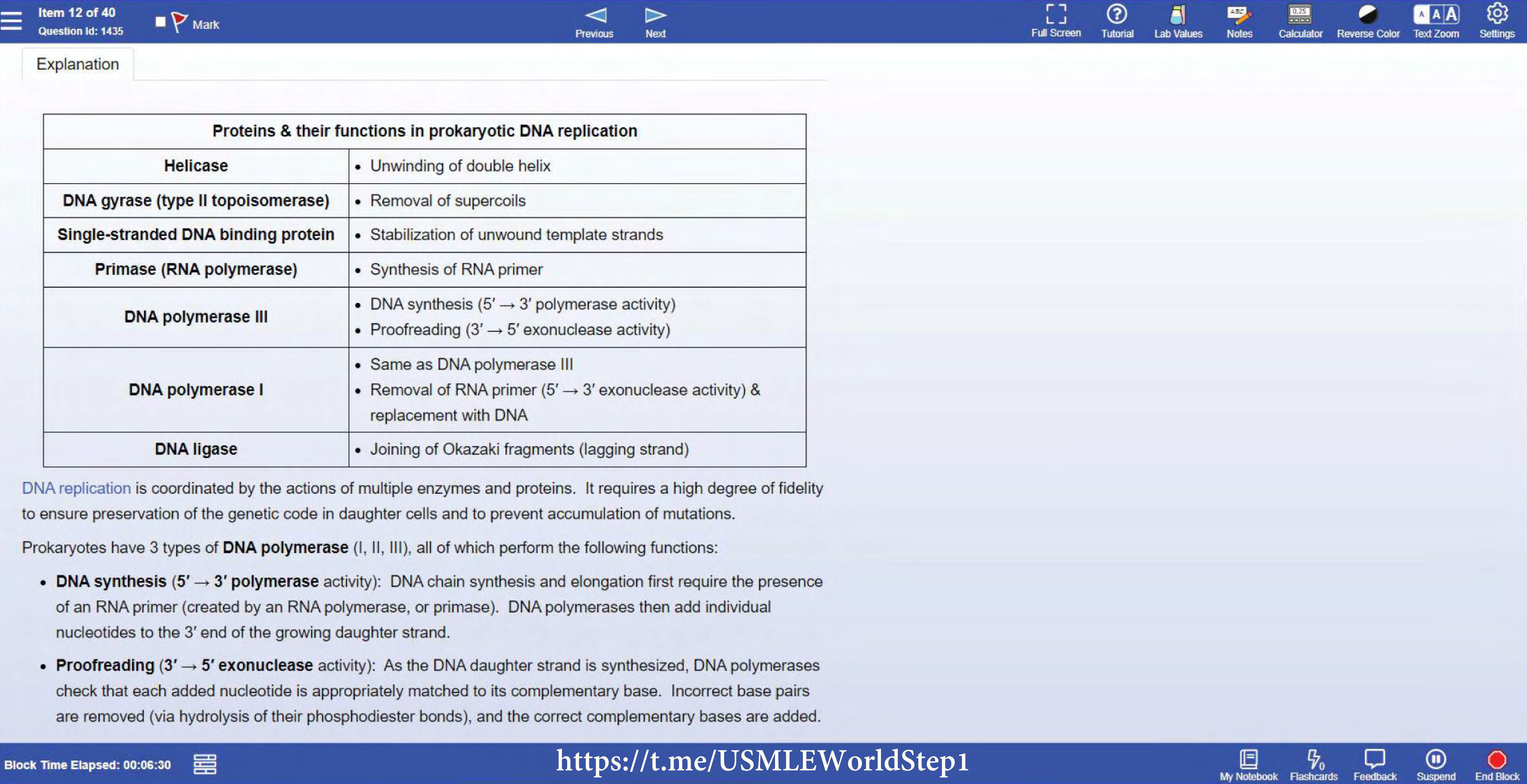
Item 12 of 40
Question Id: 1435
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Proteins & their functions in prokaryotic DNA replication	
Helicase	• Unwinding of double helix
DNA gyrase (type II topoisomerase)	• Removal of supercoils
Single-stranded DNA binding protein	• Stabilization of unwound template strands
Primase (RNA polymerase)	• Synthesis of RNA primer
DNA polymerase III	• DNA synthesis (5′ → 3′ polymerase activity) • Proofreading (3′ → 5′ exonuclease activity)
DNA polymerase I	• Same as DNA polymerase III • Removal of RNA primer (5′ → 3′ exonuclease activity) & replacement with DNA
DNA ligase	• Joining of Okazaki fragments (lagging strand)

DNA replication is coordinated by the actions of multiple enzymes and proteins. It requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells and to prevent accumulation of mutations.

Prokaryotes have 3 types of **DNA polymerase** (I, II, III), all of which perform the following functions:

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Feedback
Suspend
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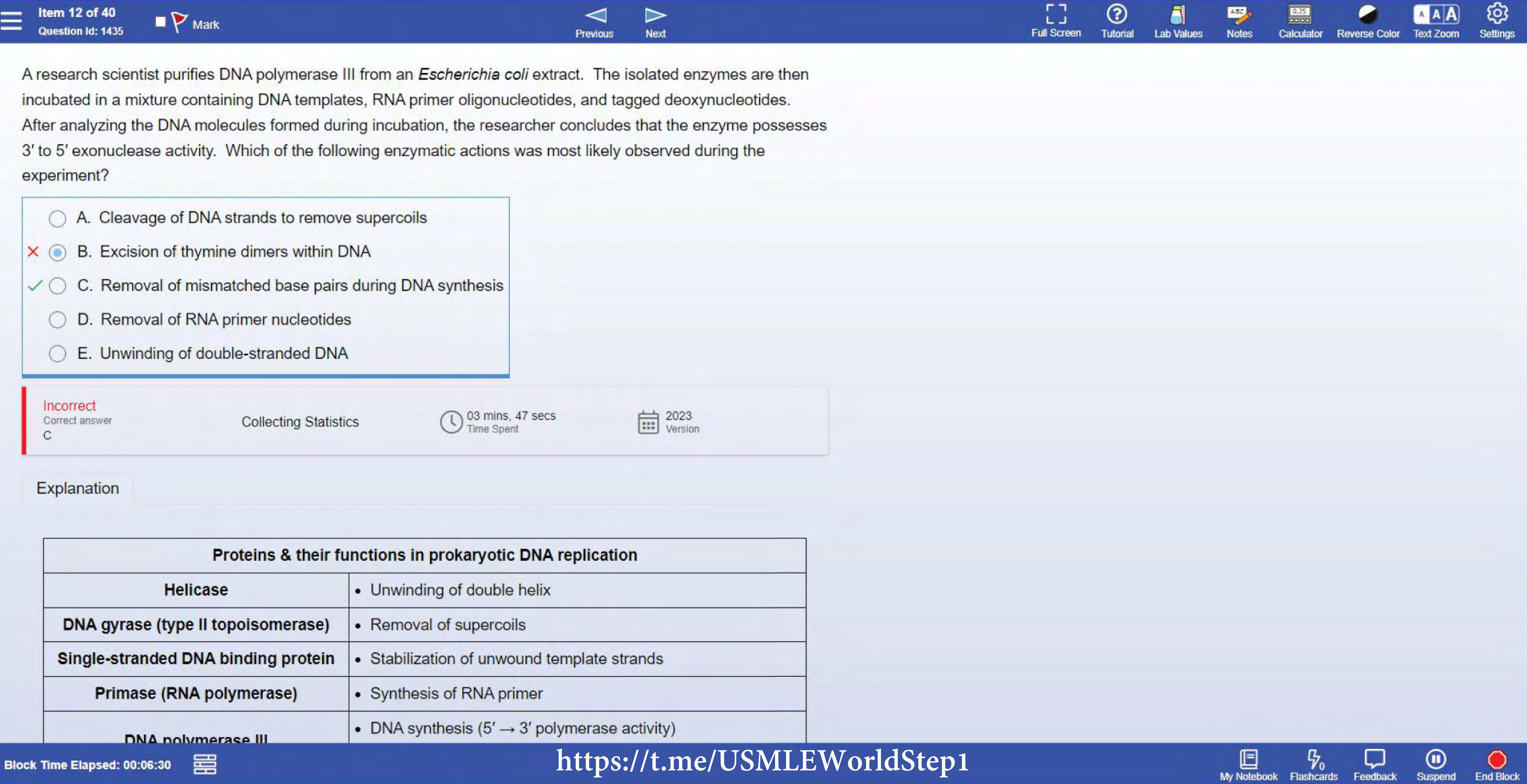
Item 12 of 40
Question Id: 1435
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist purifies DNA polymerase III from an *Escherichia coli* extract. The isolated enzymes are then incubated in a mixture containing DNA templates, RNA primer oligonucleotides, and tagged deoxynucleotides. After analyzing the DNA molecules formed during incubation, the researcher concludes that the enzyme possesses 3′ to 5′ exonuclease activity. Which of the following enzymatic actions was most likely observed during the experiment?

○ A. Cleavage of DNA strands to remove supercoils

✗ ● B. Excision of thymine dimers within DNA

✓ ○ C. Removal of mismatched base pairs during DNA synthesis

○ D. Removal of RNA primer nucleotides

○ E. Unwinding of double-stranded DNA

Incorrect
Correct answer
C

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Time Spent

2023
Version

Explanation

Proteins & their functions in prokaryotic DNA replication	
Helicase	• Unwinding of double helix
DNA gyrase (type II topoisomerase)	• Removal of supercoils
Single-stranded DNA binding protein	• Stabilization of unwound template strands
Primase (RNA polymerase)	• Synthesis of RNA primer
DNA polymerase III	• DNA synthesis (5′ → 3′ polymerase activity)

Block Time Elapsed: 00:06:30
My Notebook
Flashcards
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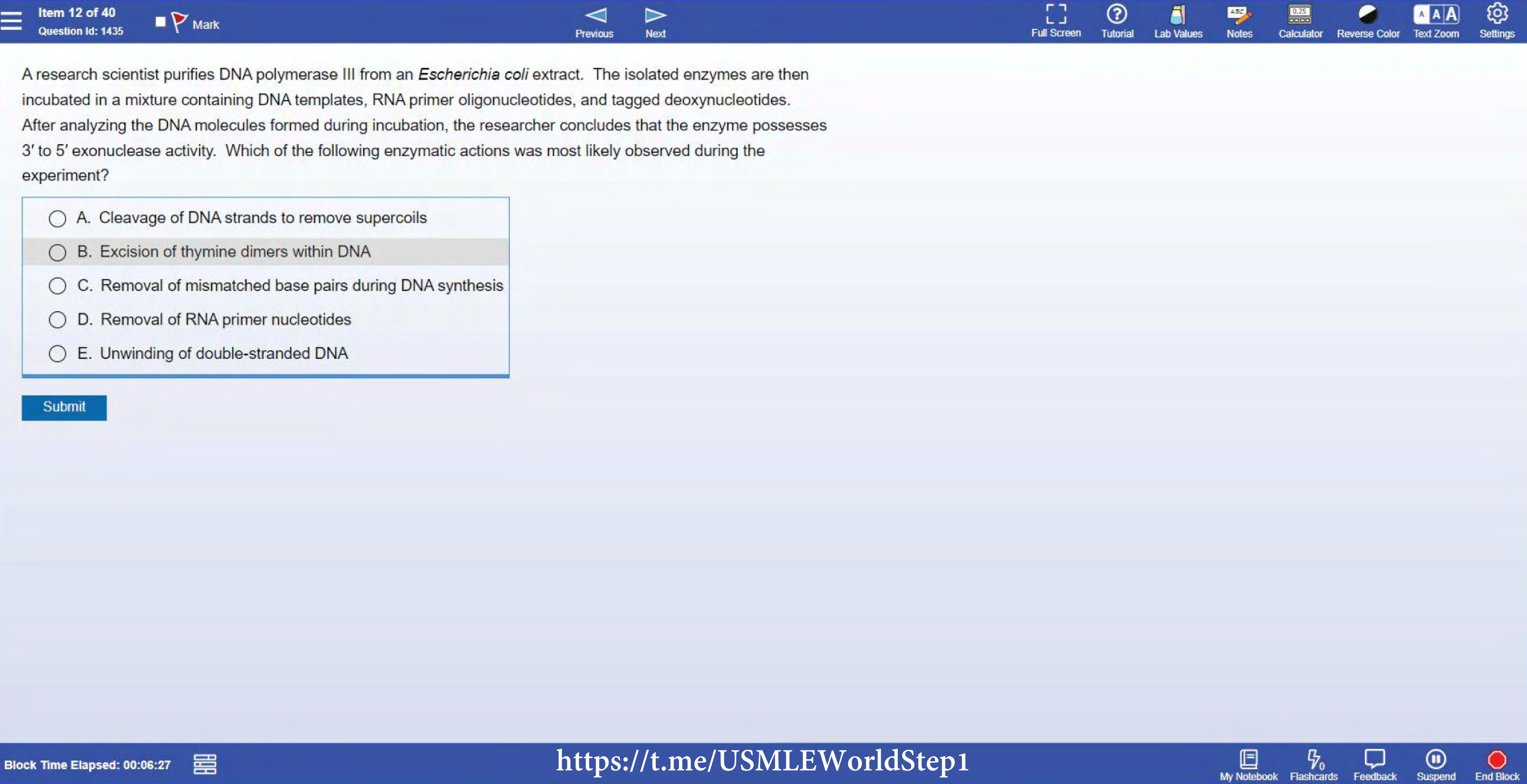
Item 12 of 40
Question Id: 1435
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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- ○ B. Excision of thymine dimers within DNA
- ○ C. Removal of mismatched base pairs during DNA synthesis
- ○ D. Removal of RNA primer nucleotides
- ○ E. Unwinding of double-stranded DNA

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My Notebook
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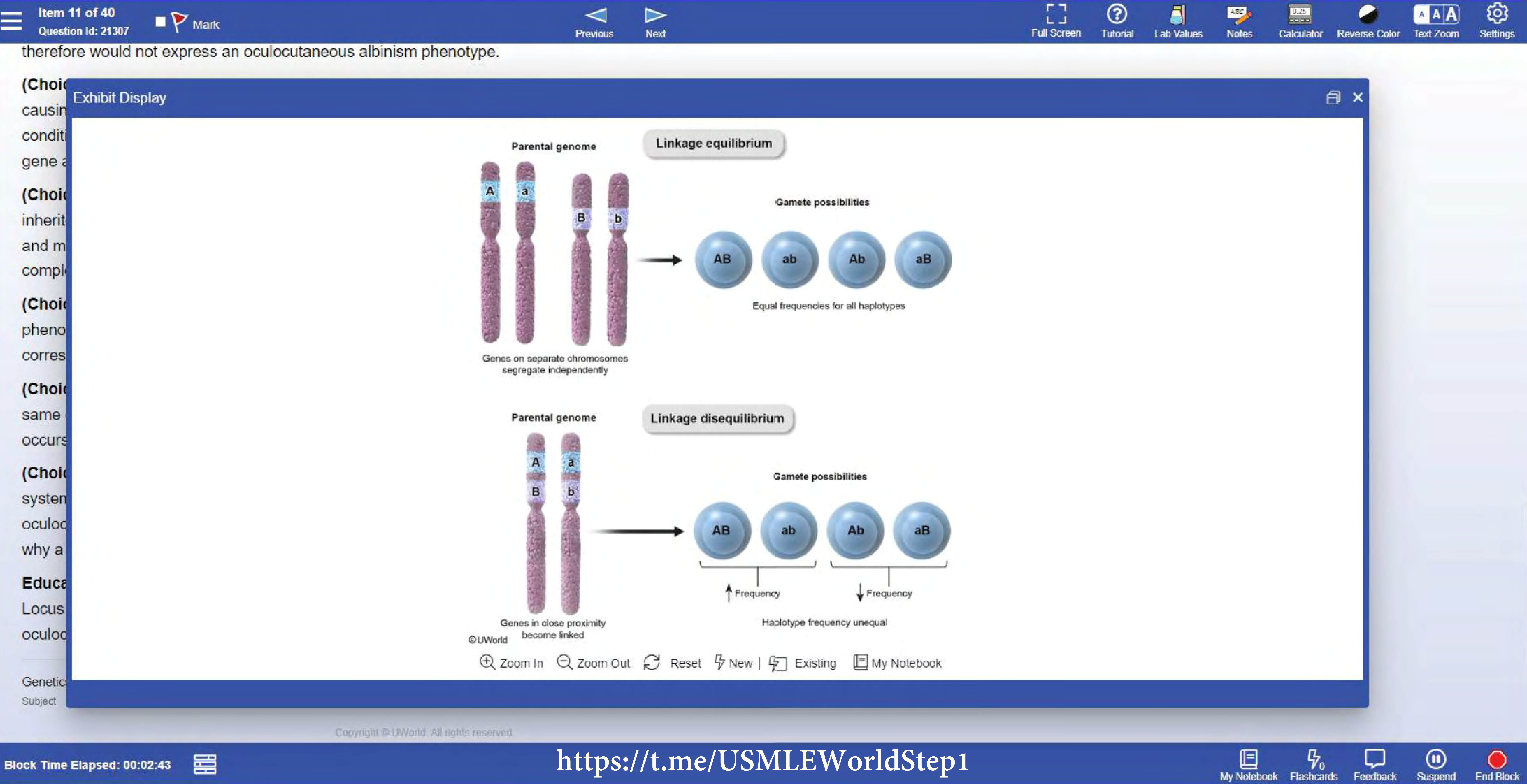
Item 11 of 40
Question Id: 21307
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
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Settings
Exhibit Display
Parental genome
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Gamete possibilities
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Haplotype frequency unequal
Genes in close proximity become linked
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therefore would not express an oculocutaneous albinism phenotype.

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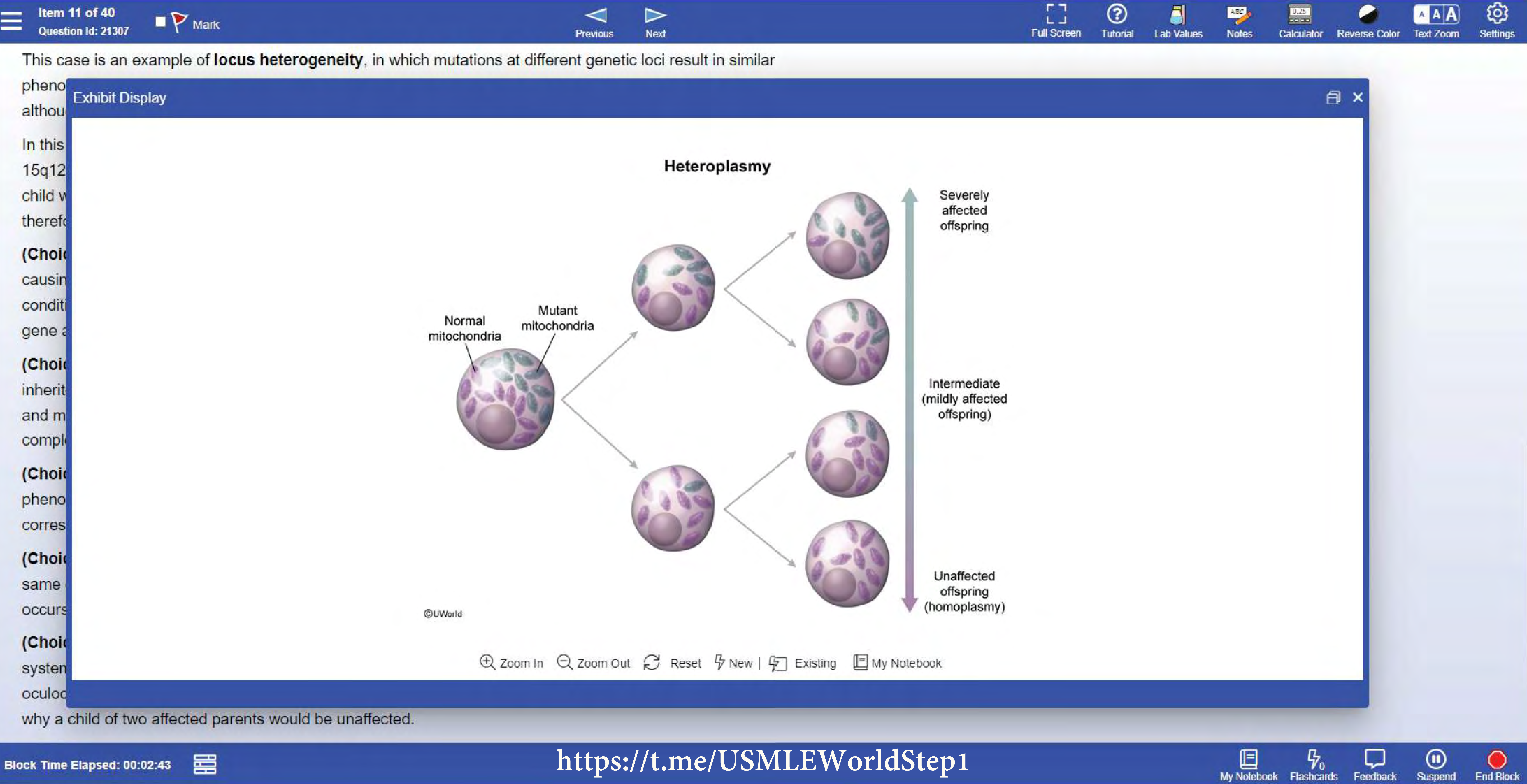

Item 11 of 40
Question Id: 21307
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
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Reverse Color
Text Zoom
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This case is an example of **locus heterogeneity**, in which mutations at different genetic loci result in similar

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why a child of two affected parents would be unaffected.

Exhibit Display
Heteroplasmy
Normal mitochondria
Mutant mitochondria
Severely affected offspring
Intermediate (mildly affected offspring)
Unaffected offspring (homoplasmy)
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New
Existing
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Block Time Elapsed: 00:02:43
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This case is an example of **locus heterogeneity**, in which mutations at different genetic loci result in similar

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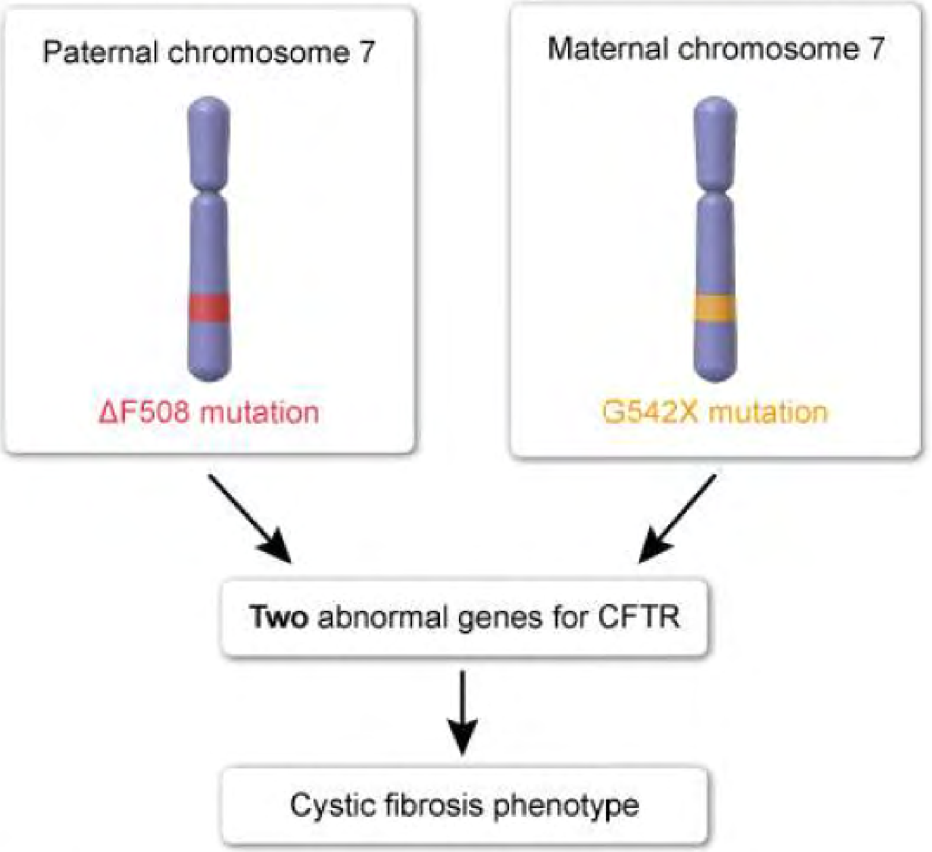
why a child of two affected parents would be unaffected.

Exhibit Display

Allelic heterogeneity in cystic fibrosis

Different mutations at the same genetic locus result in the same phenotype.


Paternal chromosome 7
ΔF508 mutation
Maternal chromosome 7
G542X mutation
Two abnormal genes for CFTR
Cystic fibrosis phenotype

CFTR = cystic fibrosis transmembrane conductance regulator.

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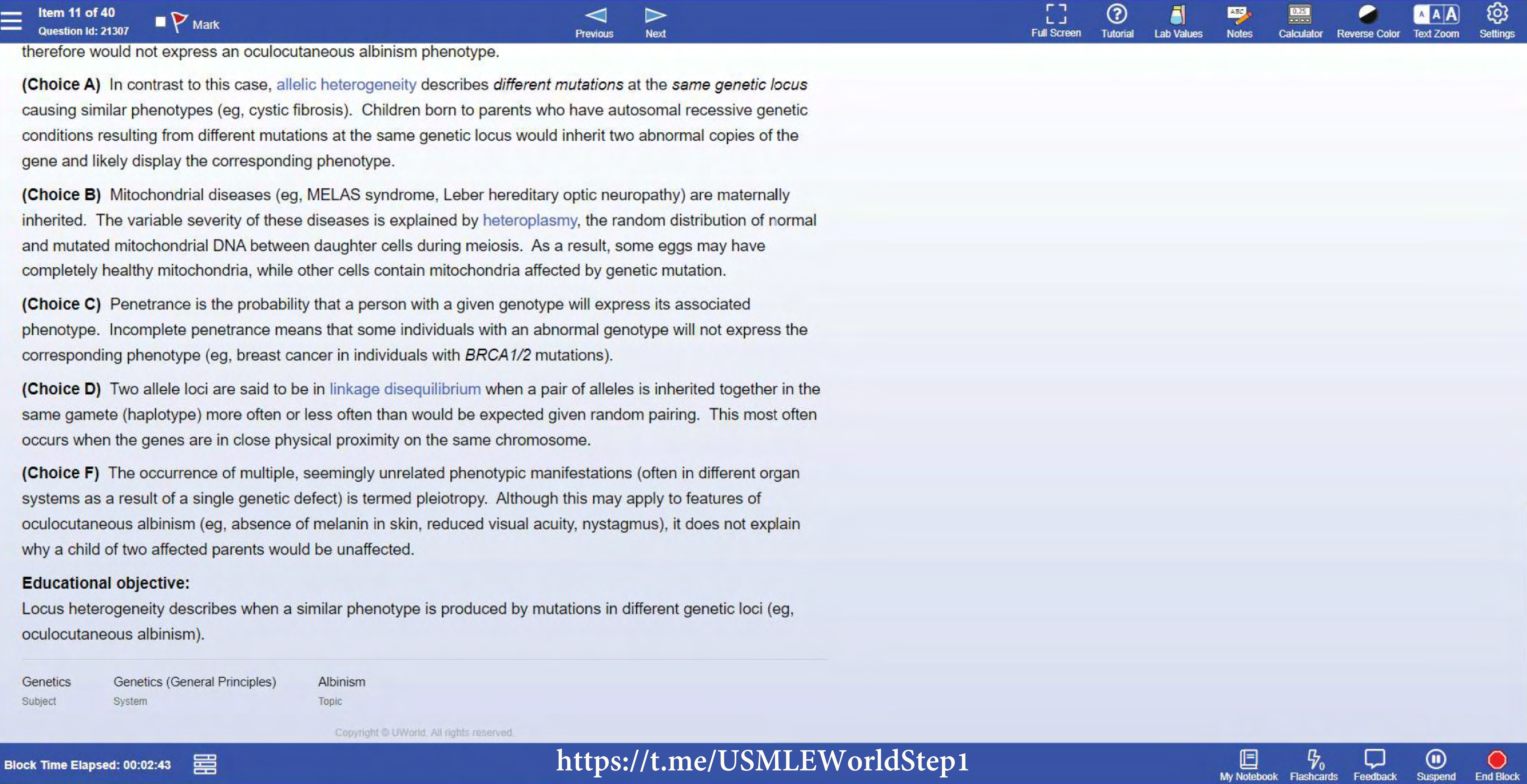

therefore would not express an oculocutaneous albinism phenotype.

(Choice A) In contrast to this case, allelic heterogeneity describes *different mutations* at the *same genetic locus* causing similar phenotypes (eg, cystic fibrosis). Children born to parents who have autosomal recessive genetic conditions resulting from different mutations at the same genetic locus would inherit two abnormal copies of the gene and likely display the corresponding phenotype.

(Choice B) Mitochondrial diseases (eg, MELAS syndrome, Leber hereditary optic neuropathy) are maternally inherited. The variable severity of these diseases is explained by heteroplasmy, the random distribution of normal and mutated mitochondrial DNA between daughter cells during meiosis. As a result, some eggs may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation.

(Choice C) Penetrance is the probability that a person with a given genotype will express its associated phenotype. Incomplete penetrance means that some individuals with an abnormal genotype will not express the corresponding phenotype (eg, breast cancer in individuals with *BRCA1/2* mutations).

(Choice D) Two allele loci are said to be in linkage disequilibrium when a pair of alleles is inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

(Choice F) The occurrence of multiple, seemingly unrelated phenotypic manifestations (often in different organ systems as a result of a single genetic defect) is termed pleiotropy. Although this may apply to features of oculocutaneous albinism (eg, absence of melanin in skin, reduced visual acuity, nystagmus), it does not explain why a child of two affected parents would be unaffected.

Educational objective:

Locus heterogeneity describes when a similar phenotype is produced by mutations in different genetic loci (eg, oculocutaneous albinism).

Genetics	Genetics (General Principles)	Albinism
Subject	System	Topic

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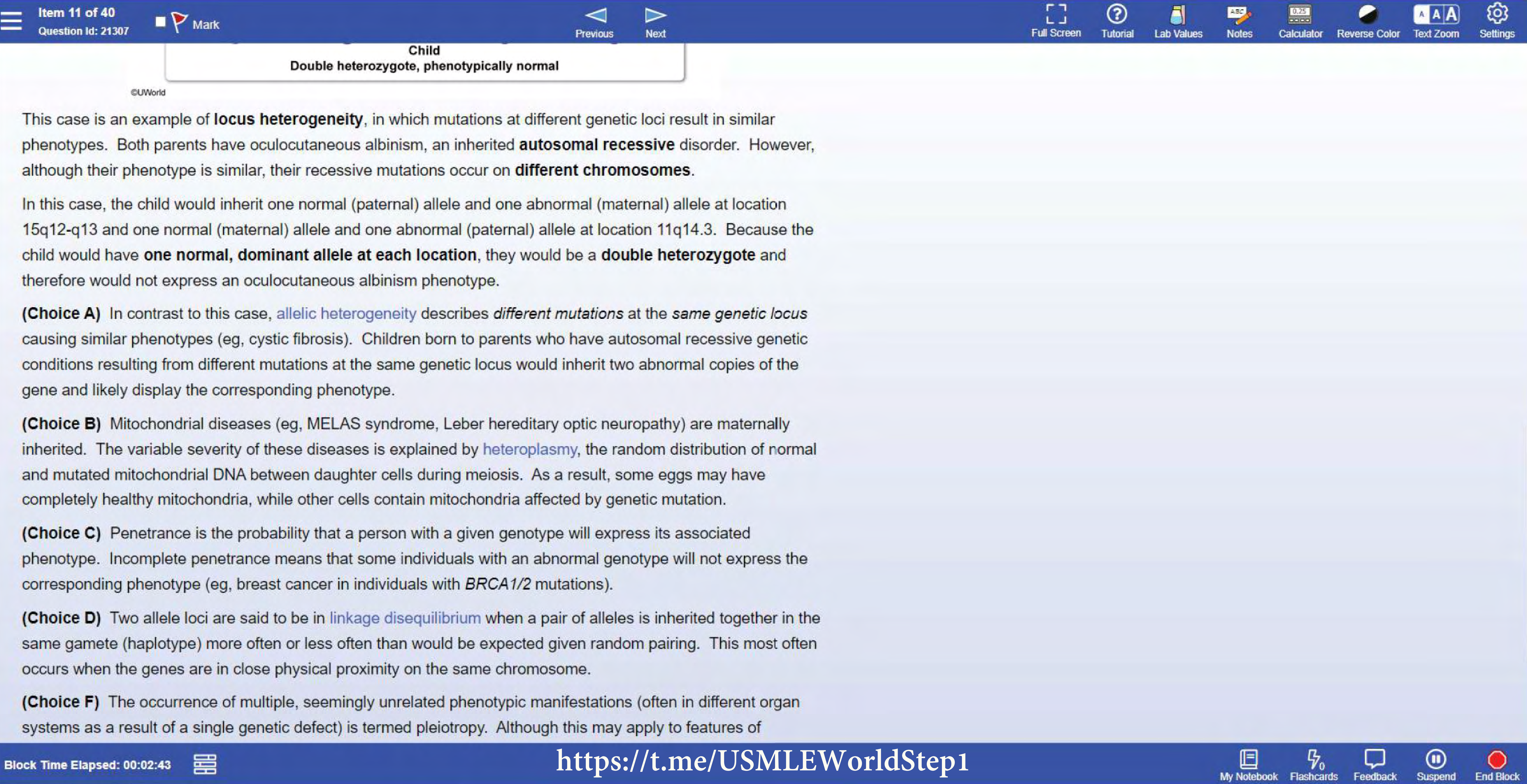

Child
Double heterozygote, phenotypically normal

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This case is an example of **locus heterogeneity**, in which mutations at different genetic loci result in similar phenotypes. Both parents have oculocutaneous albinism, an inherited **autosomal recessive** disorder. However, although their phenotype is similar, their recessive mutations occur on **different chromosomes**.

In this case, the child would inherit one normal (paternal) allele and one abnormal (maternal) allele at location 15q12-q13 and one normal (maternal) allele and one abnormal (paternal) allele at location 11q14.3. Because the child would have **one normal, dominant allele at each location**, they would be a **double heterozygote** and therefore would not express an oculocutaneous albinism phenotype.

(Choice A) In contrast to this case, allelic heterogeneity describes *different mutations* at the *same genetic locus* causing similar phenotypes (eg, cystic fibrosis). Children born to parents who have autosomal recessive genetic conditions resulting from different mutations at the same genetic locus would inherit two abnormal copies of the gene and likely display the corresponding phenotype.

(Choice B) Mitochondrial diseases (eg, MELAS syndrome, Leber hereditary optic neuropathy) are maternally inherited. The variable severity of these diseases is explained by heteroplasmy, the random distribution of normal and mutated mitochondrial DNA between daughter cells during meiosis. As a result, some eggs may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation.

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(Choice F) The occurrence of multiple, seemingly unrelated phenotypic manifestations (often in different organ systems as a result of a single genetic defect) is termed pleiotropy. Although this may apply to features of

✓ ○ E. Locus heterogeneity (47%)

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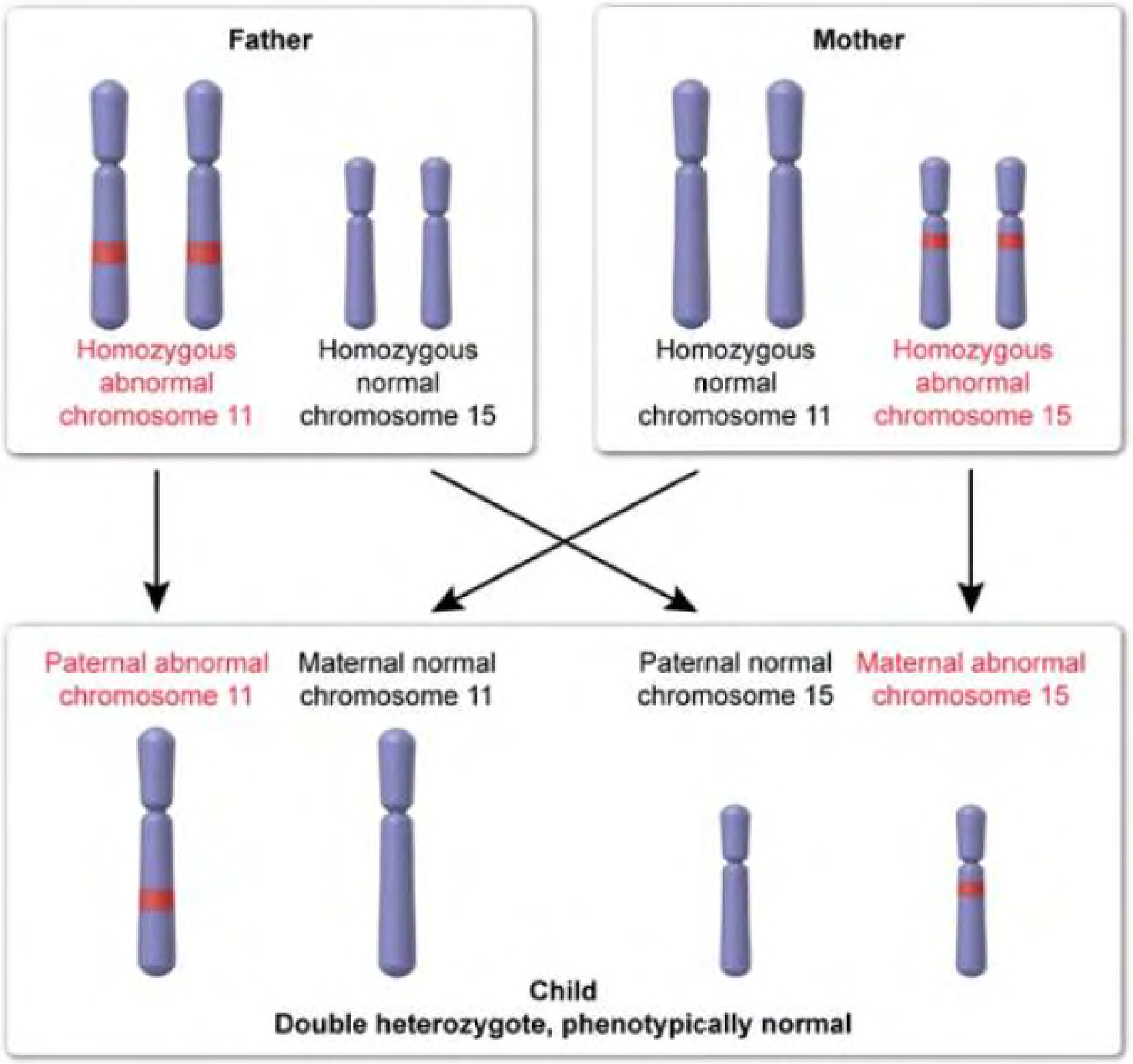
Locus heterogeneity in oculocutaneous albinism

Mutations at different genetic loci result in similar phenotypes.


Father
Homozygous abnormal chromosome 11
Homozygous normal chromosome 15
Mother
Homozygous normal chromosome 11
Homozygous abnormal chromosome 15
Paternal abnormal chromosome 11
Maternal normal chromosome 11
Paternal normal chromosome 15
Maternal abnormal chromosome 15
Child
Double heterozygote, phenotypically normal

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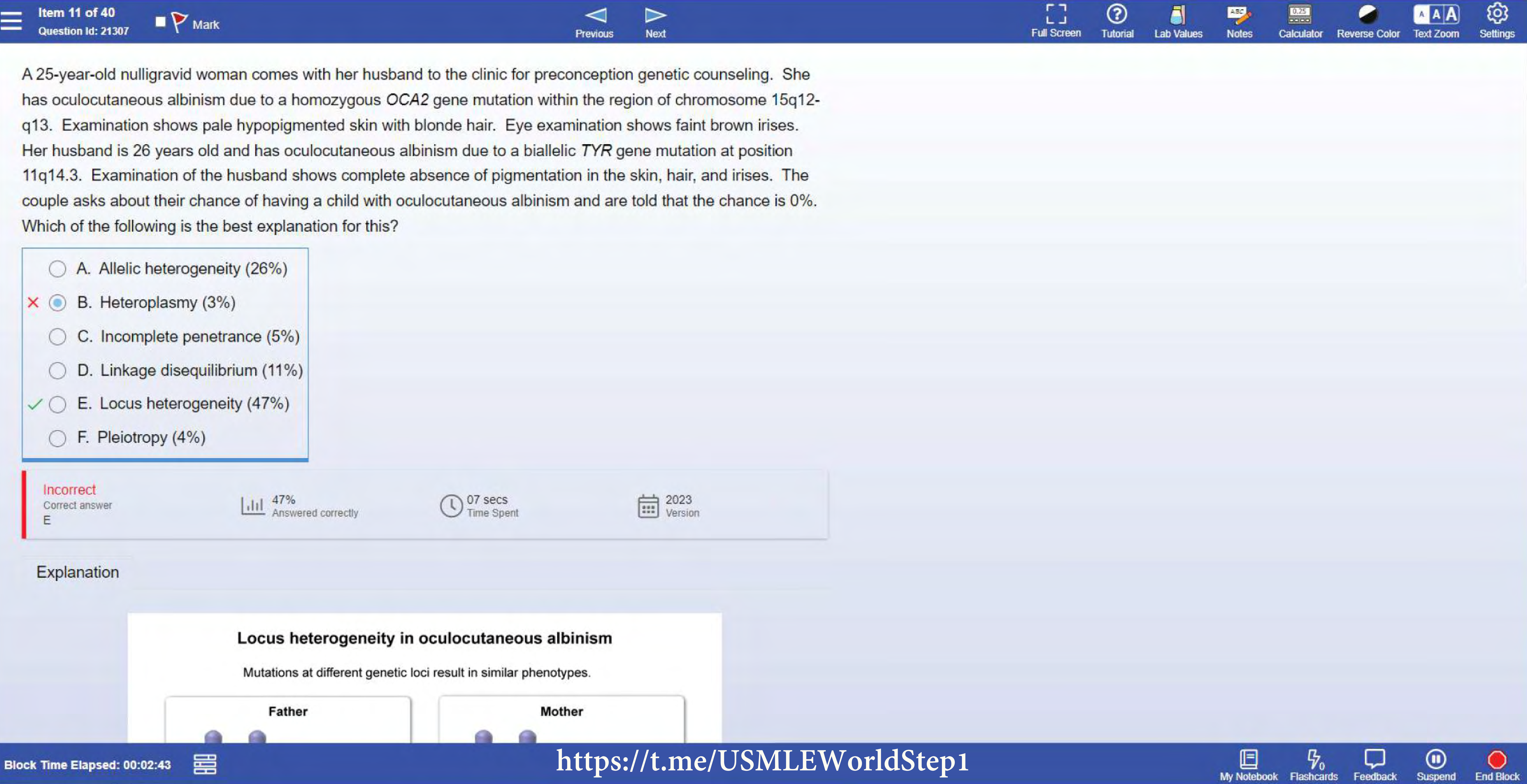
Zoom In Zoom Out Reset New | Existing My Notebook


Item 11 of 40
Question Id: 21307
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 25-year-old nulligravid woman comes with her husband to the clinic for preconception genetic counseling. She has oculocutaneous albinism due to a homozygous *OCA2* gene mutation within the region of chromosome 15q12-q13. Examination shows pale hypopigmented skin with blonde hair. Eye examination shows faint brown irises. Her husband is 26 years old and has oculocutaneous albinism due to a biallelic *TYR* gene mutation at position 11q14.3. Examination of the husband shows complete absence of pigmentation in the skin, hair, and irises. The couple asks about their chance of having a child with oculocutaneous albinism and are told that the chance is 0%. Which of the following is the best explanation for this?

- ○ A. Allelic heterogeneity (26%)
- ✗ ● B. Heteroplasmy (3%)
- ○ C. Incomplete penetrance (5%)
- ○ D. Linkage disequilibrium (11%)
- ✓ ○ E. Locus heterogeneity (47%)
- ○ F. Pleiotropy (4%)

Incorrect
Correct answer
E

47%
Answered correctly

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2023
Version

Explanation

Locus heterogeneity in oculocutaneous albinism

Mutations at different genetic loci result in similar phenotypes.

Father
Mother
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Flashcards
Feedback
Suspend
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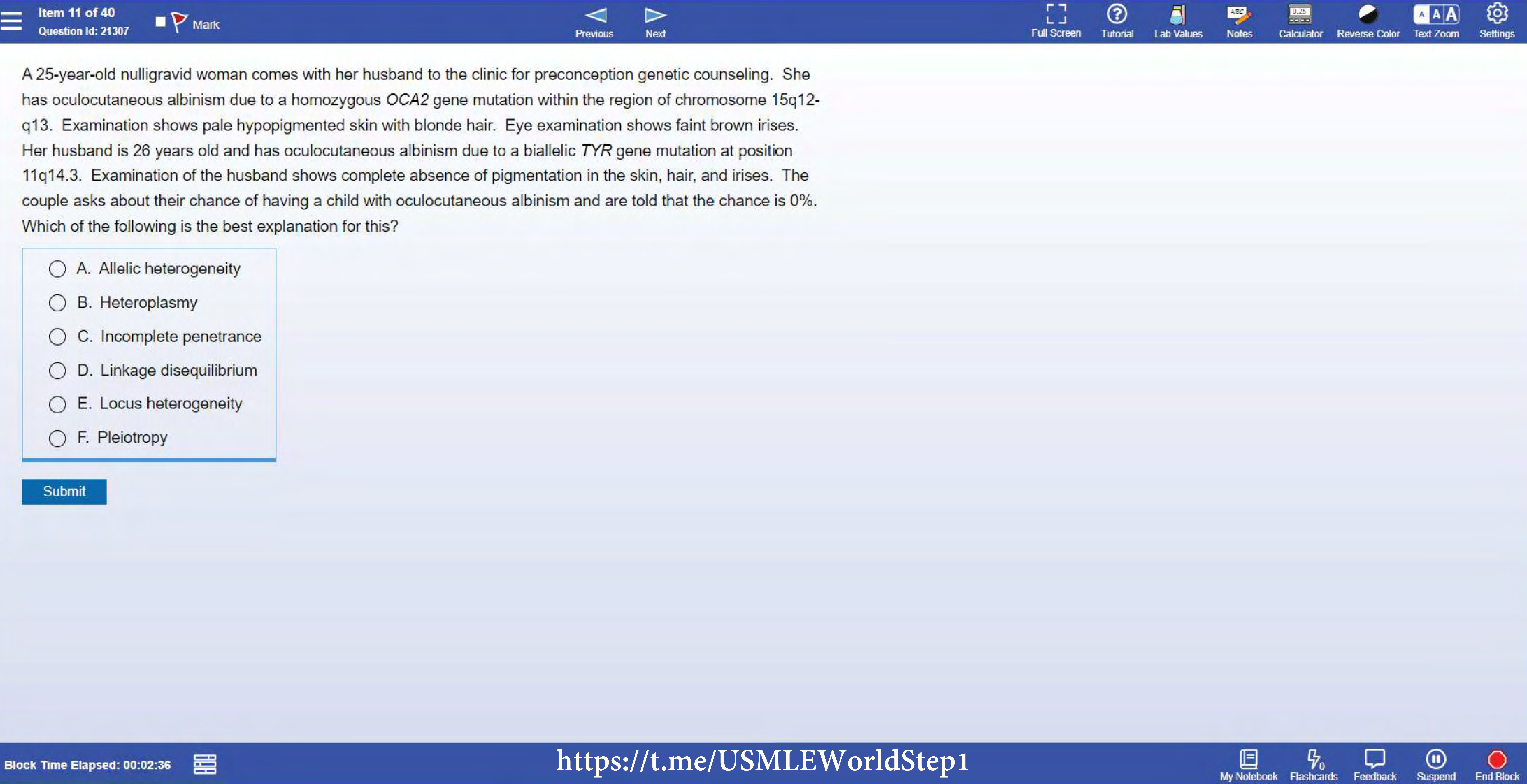
Item 11 of 40
Question Id: 21307
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 25-year-old nulligravid woman comes with her husband to the clinic for preconception genetic counseling. She has oculocutaneous albinism due to a homozygous *OCA2* gene mutation within the region of chromosome 15q12-q13. Examination shows pale hypopigmented skin with blonde hair. Eye examination shows faint brown irises. Her husband is 26 years old and has oculocutaneous albinism due to a biallelic *TYR* gene mutation at position 11q14.3. Examination of the husband shows complete absence of pigmentation in the skin, hair, and irises. The couple asks about their chance of having a child with oculocutaneous albinism and are told that the chance is 0%. Which of the following is the best explanation for this?

○ A. Allelic heterogeneity
○ B. Heteroplasmy
○ C. Incomplete penetrance
○ D. Linkage disequilibrium
○ E. Locus heterogeneity
○ F. Pleiotropy

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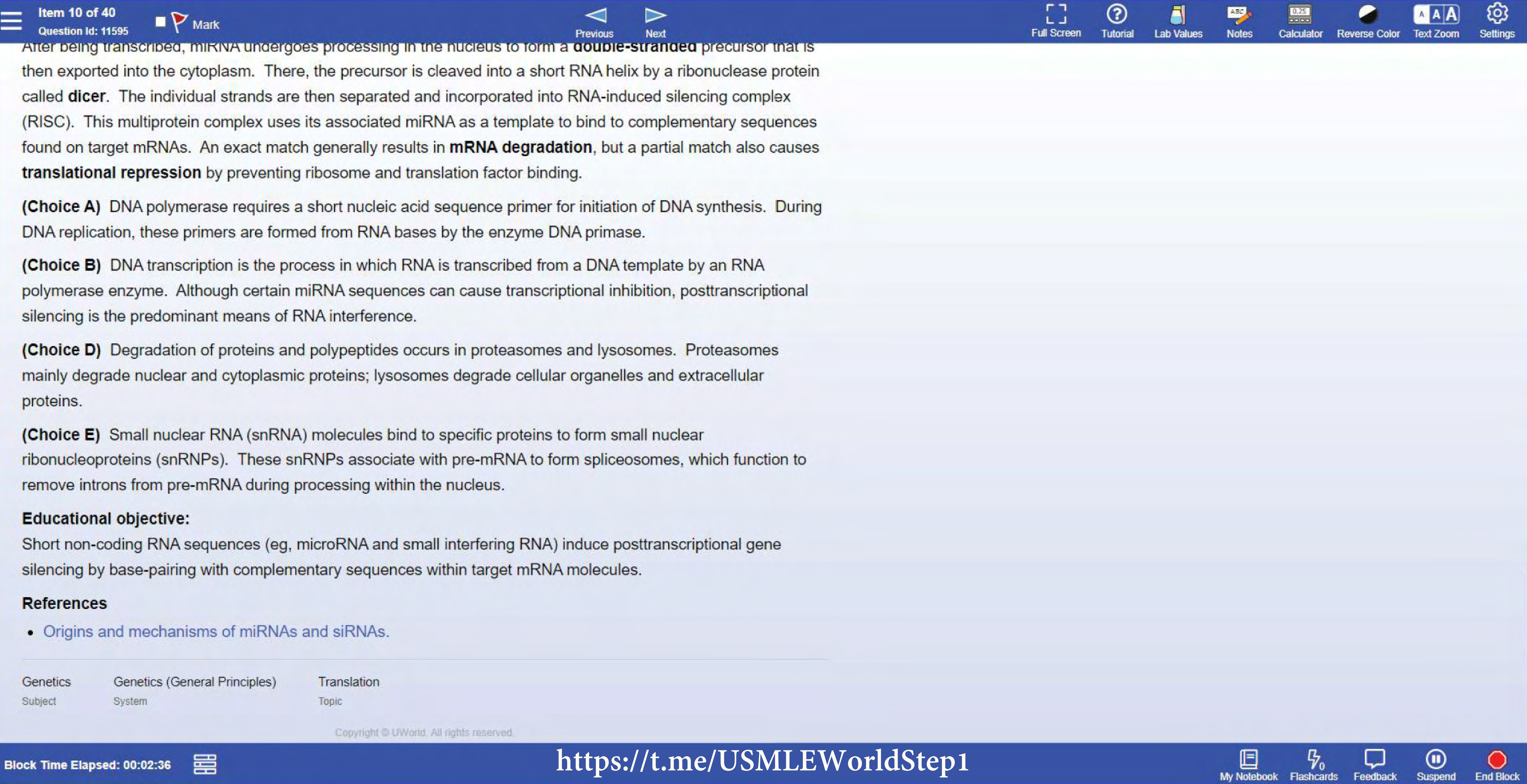
My Notebook
Flashcards
Feedback
Suspend
End Block



After being transcribed, miRNA undergoes processing in the nucleus to form a **double-stranded** precursor that is then exported into the cytoplasm. There, the precursor is cleaved into a short RNA helix by a ribonuclease protein called **dicer**. The individual strands are then separated and incorporated into RNA-induced silencing complex (RISC). This multiprotein complex uses its associated miRNA as a template to bind to complementary sequences found on target mRNAs. An exact match generally results in **mRNA degradation**, but a partial match also causes **translational repression** by preventing ribosome and translation factor binding.

(Choice A) DNA polymerase requires a short nucleic acid sequence primer for initiation of DNA synthesis. During DNA replication, these primers are formed from RNA bases by the enzyme DNA primase.

(Choice B) DNA transcription is the process in which RNA is transcribed from a DNA template by an RNA polymerase enzyme. Although certain miRNA sequences can cause transcriptional inhibition, posttranscriptional silencing is the predominant means of RNA interference.

(Choice D) Degradation of proteins and polypeptides occurs in proteasomes and lysosomes. Proteasomes mainly degrade nuclear and cytoplasmic proteins; lysosomes degrade cellular organelles and extracellular proteins.

(Choice E) Small nuclear RNA (snRNA) molecules bind to specific proteins to form small nuclear ribonucleoproteins (snRNPs). These snRNPs associate with pre-mRNA to form spliceosomes, which function to remove introns from pre-mRNA during processing within the nucleus.

Educational objective:

Short non-coding RNA sequences (eg, microRNA and small interfering RNA) induce posttranscriptional gene silencing by base-pairing with complementary sequences within target mRNA molecules.

References

- Origins and mechanisms of miRNAs and siRNAs.

Genetics	Genetics (General Principles)	Translation
Subject	System	Topic

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mRNA cleavage
Translation repression

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The results of the western blot show that the treated cell line produces less c-myc protein. This is most likely due to RNA interference, a mechanism by which short (20-30 base pair) **double-stranded RNA** sequences induce **posttranscriptional gene silencing**.

Silencing RNA includes both small interfering RNA (siRNA) and microRNA (miRNA). The human genome encodes over 1000 miRNA genes, each one capable of repressing hundreds of target genes; altered expression of miRNA genes are involved in the development of many diseases, including hematologic and solid malignancies. In addition, synthetic siRNA sequences can be introduced into cells to silence specific pathogenic genes (eg, c-Myc oncogene) and are being explored as possible **therapeutic agents**.

After being transcribed, miRNA undergoes processing in the nucleus to form a **double-stranded** precursor that is then exported into the cytoplasm. There, the precursor is cleaved into a short RNA helix by a ribonuclease protein called **dicer**. The individual strands are then separated and incorporated into RNA-induced silencing complex (RISC). This multiprotein complex uses its associated miRNA as a template to bind to complementary sequences found on target mRNAs. An exact match generally results in **mRNA degradation**, but a partial match also causes **translational repression** by preventing ribosome and translation factor binding.

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Item 10 of 40
Question Id: 11595

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Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

Correct answer
C

Answered correctly

Time Spent

Version

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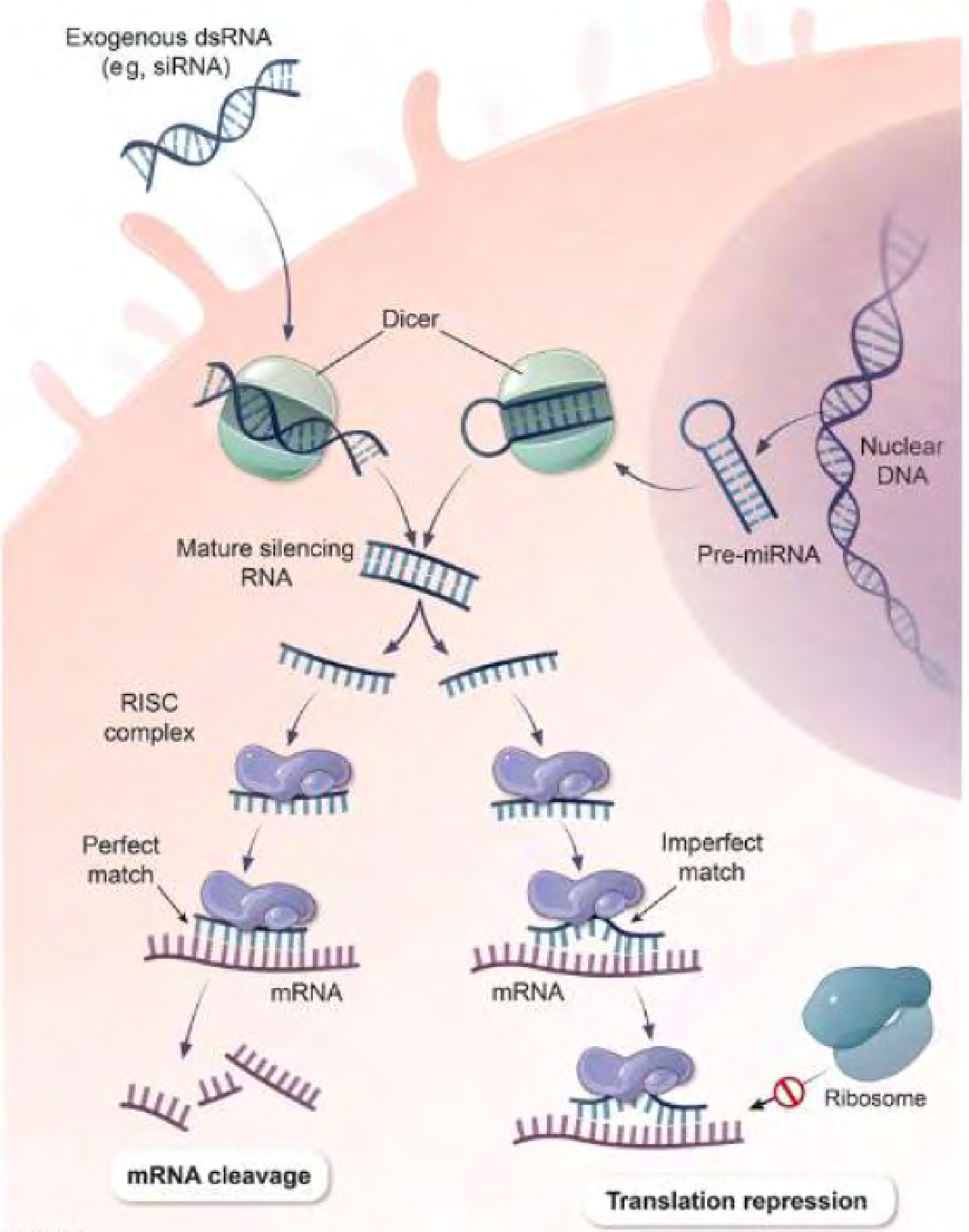
Exhibit Display

RNA interference



Exogenous dsRNA
(eg, siRNA)
Dicer
Nuclear
DNA
Pre-miRNA
Mature silencing
RNA
RISC
complex
Perfect
match
Imperfect
match
mRNA
mRNA
Ribosome
mRNA cleavage
Translation repression

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Block Time Elapsed: 00:02:36

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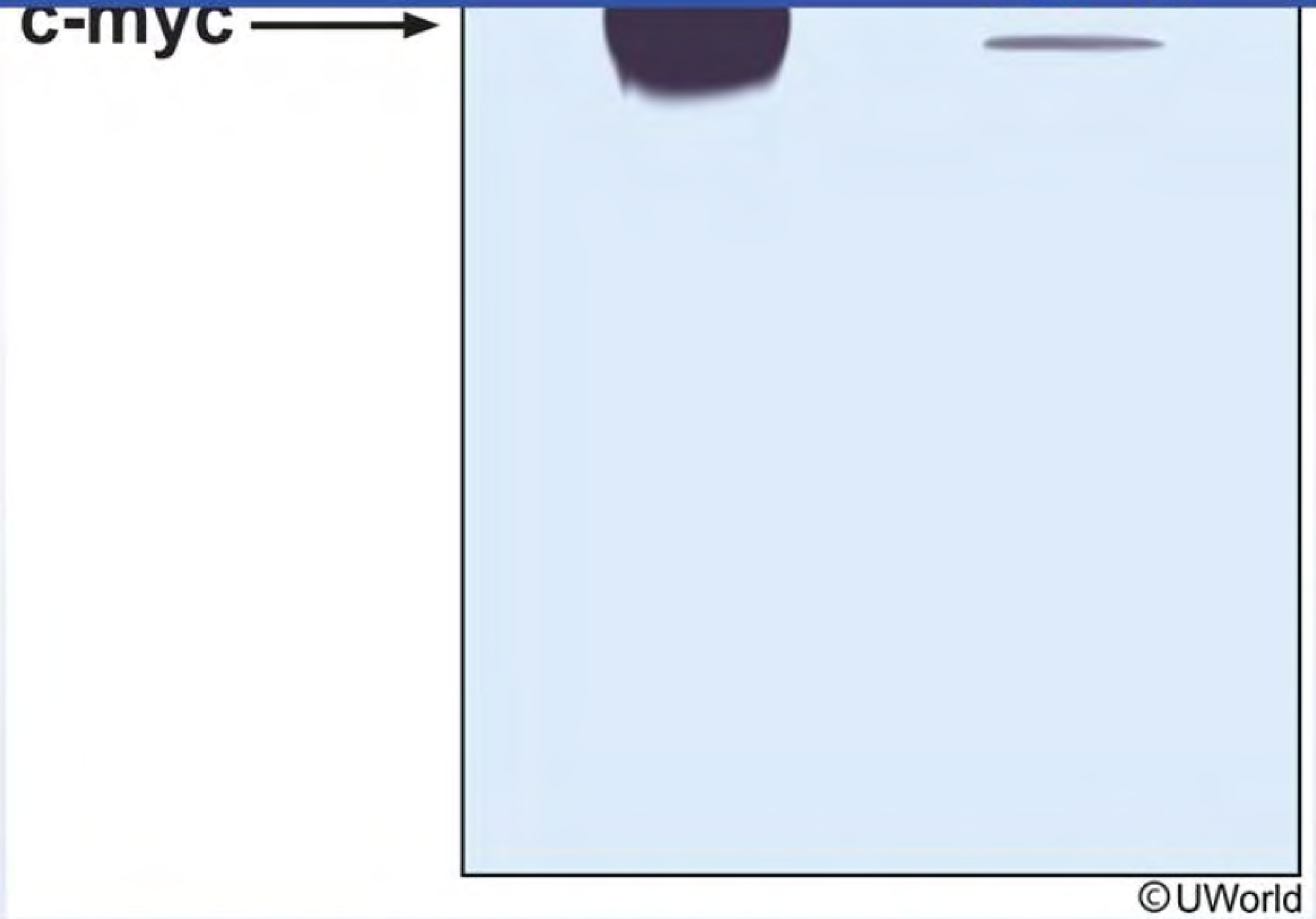

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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

- ○ A. DNA replication (8%)
- ✗ ● B. DNA transcription (17%)
- ✓ ○ C. mRNA translation (64%)
- ○ D. Proteasome activity (3%)
- ○ E. Splicing (5%)

Incorrect
Correct answer
C

64%
Answered correctly

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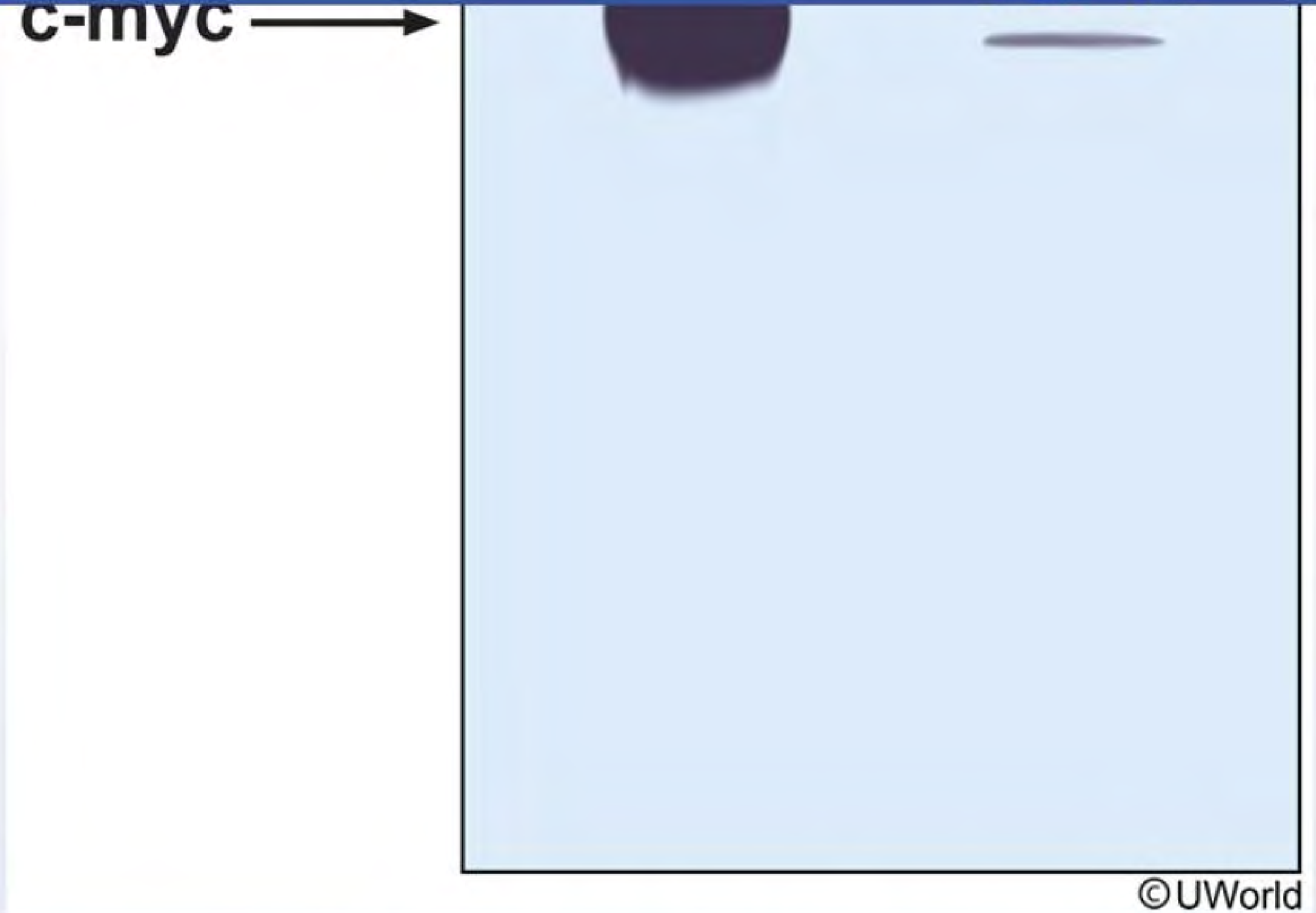
Version



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Incorrect
Correct answer
C

64%
Answered correctly

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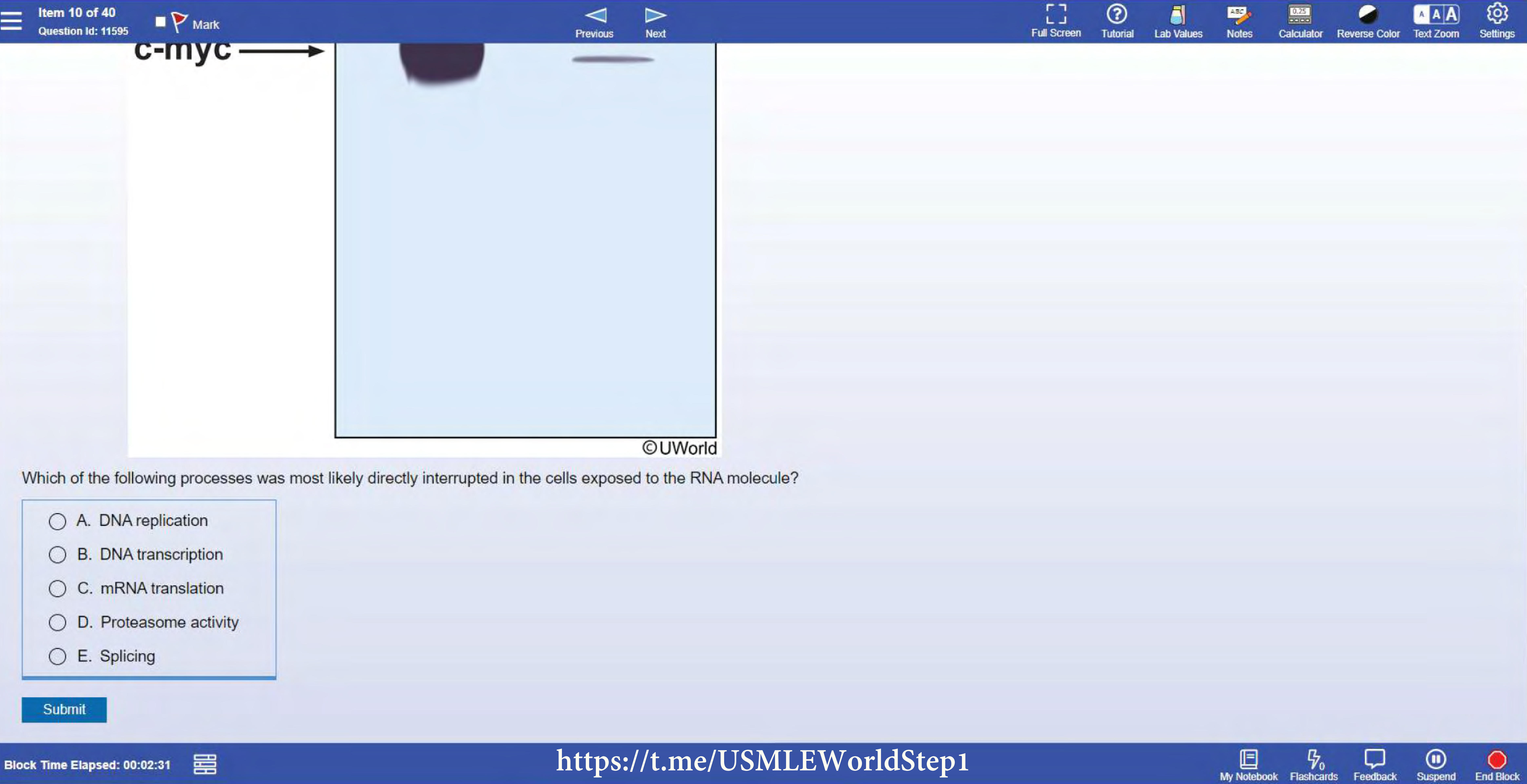
2023
Version


Item 10 of 40
Question Id: 11595
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
c-myc
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Block Time Elapsed: 00:02:31
My Notebook
Flashcards
Feedback
Suspend
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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

○ A. DNA replication
○ B. DNA transcription
○ C. mRNA translation
○ D. Proteasome activity
○ E. Splicing

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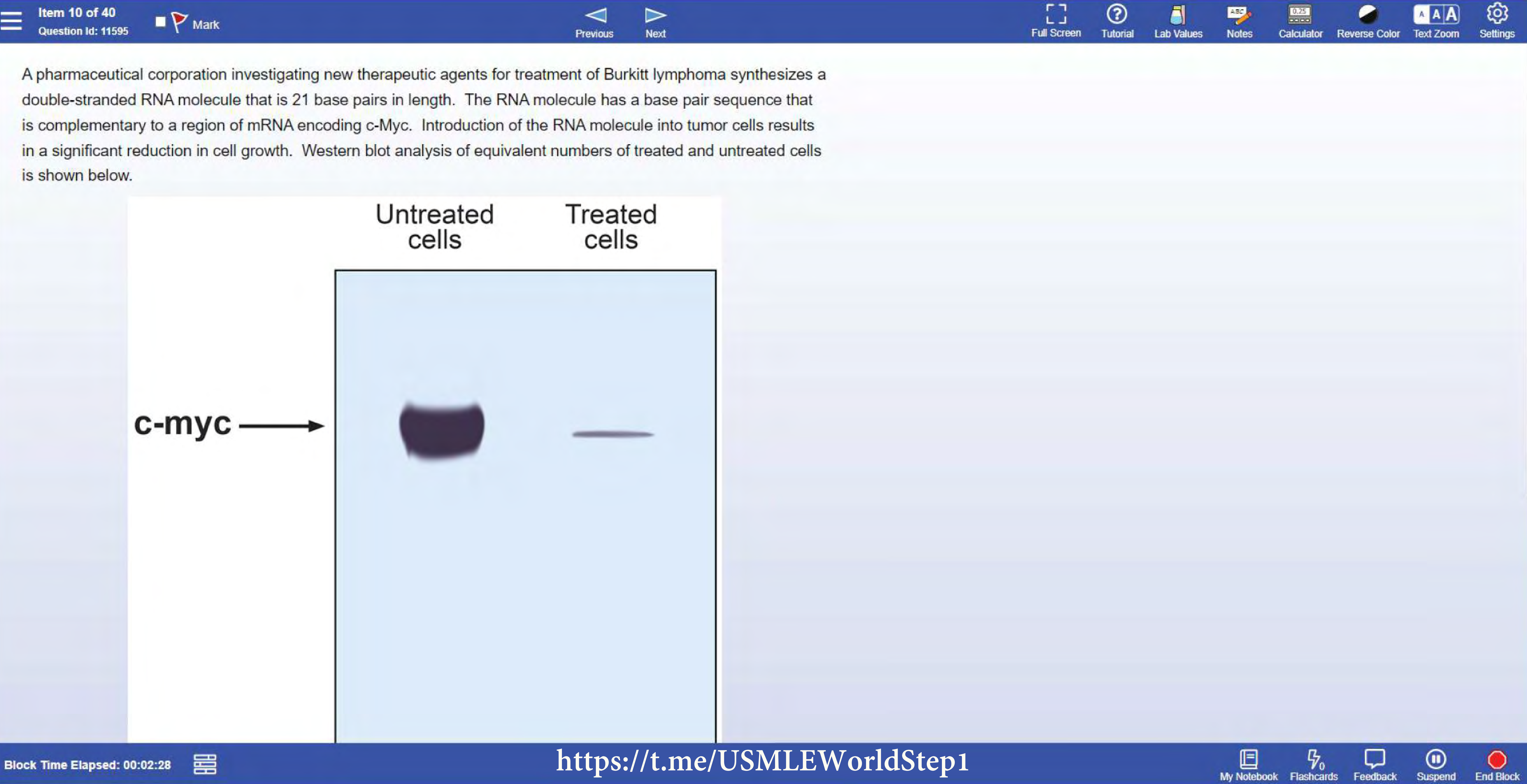

Item 10 of 40
Question Id: 11595
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A pharmaceutical corporation investigating new therapeutic agents for treatment of Burkitt lymphoma synthesizes a double-stranded RNA molecule that is 21 base pairs in length. The RNA molecule has a base pair sequence that is complementary to a region of mRNA encoding c-Myc. Introduction of the RNA molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.

Untreated cells
Treated cells
c-myc

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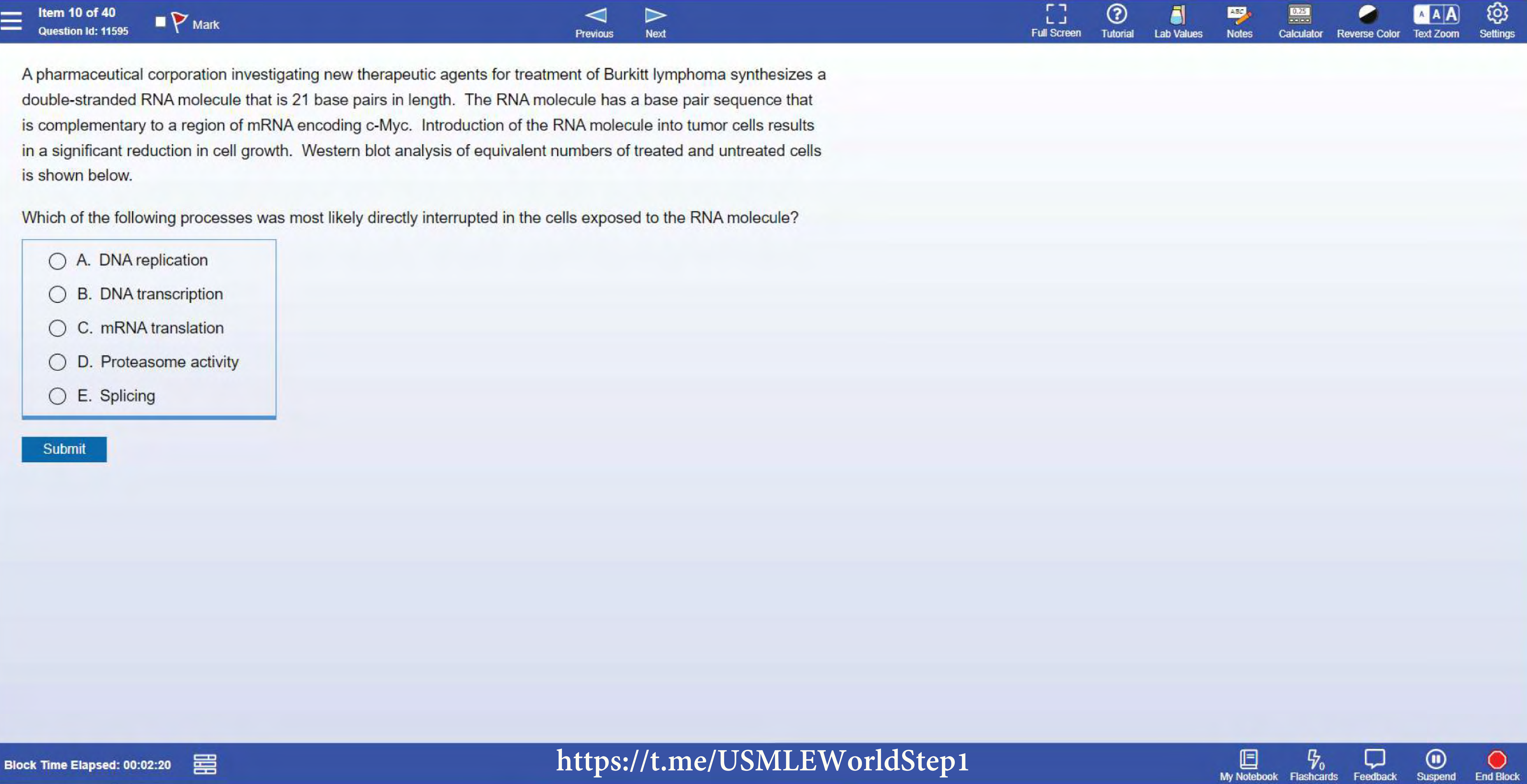
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 10 of 40
Question Id: 11595
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ B. DNA transcription
○ C. mRNA translation
○ D. Proteasome activity
○ E. Splicing

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Flashcards
Feedback
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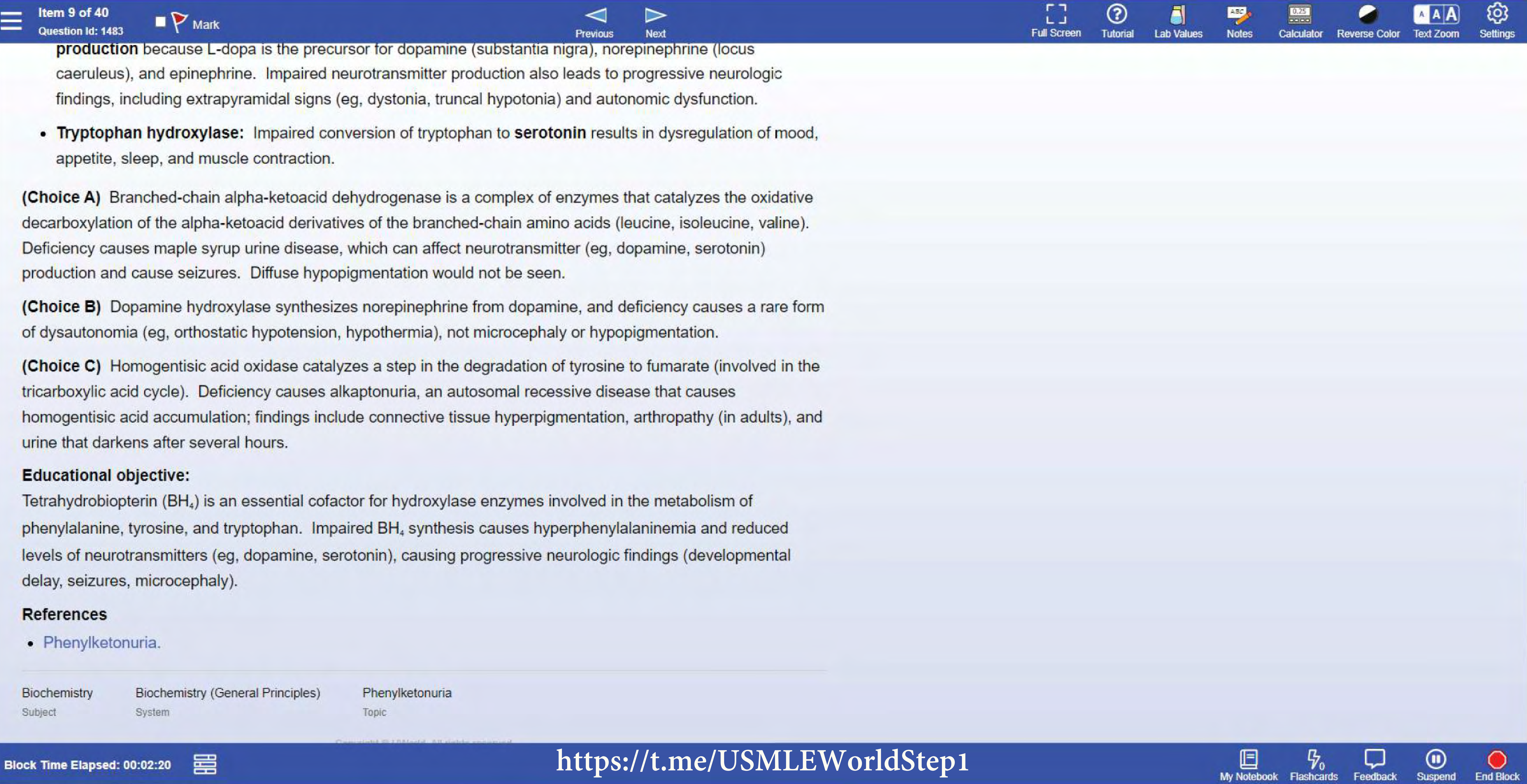

production because L-dopa is the precursor for dopamine (substantia nigra), norepinephrine (locus caeruleus), and epinephrine. Impaired neurotransmitter production also leads to progressive neurologic findings, including extrapyramidal signs (eg, dystonia, truncal hypotonia) and autonomic dysfunction.

- **Tryptophan hydroxylase:** Impaired conversion of tryptophan to **serotonin** results in dysregulation of mood, appetite, sleep, and muscle contraction.

(Choice A) Branched-chain alpha-ketoacid dehydrogenase is a complex of enzymes that catalyzes the oxidative decarboxylation of the alpha-ketoacid derivatives of the branched-chain amino acids (leucine, isoleucine, valine). Deficiency causes maple syrup urine disease, which can affect neurotransmitter (eg, dopamine, serotonin) production and cause seizures. Diffuse hypopigmentation would not be seen.

(Choice B) Dopamine hydroxylase synthesizes norepinephrine from dopamine, and deficiency causes a rare form of dysautonomia (eg, orthostatic hypotension, hypothermia), not microcephaly or hypopigmentation.

(Choice C) Homogentisic acid oxidase catalyzes a step in the degradation of tyrosine to fumarate (involved in the tricarboxylic acid cycle). Deficiency causes alkaptonuria, an autosomal recessive disease that causes homogentisic acid accumulation; findings include connective tissue hyperpigmentation, arthropathy (in adults), and urine that darkens after several hours.

Educational objective:

Tetrahydrobiopterin (BH_4) is an essential cofactor for hydroxylase enzymes involved in the metabolism of phenylalanine, tyrosine, and tryptophan. Impaired BH_4 synthesis causes hyperphenylalaninemia and reduced levels of neurotransmitters (eg, dopamine, serotonin), causing progressive neurologic findings (developmental delay, seizures, microcephaly).

References

- Phenylketonuria.

Biochemistry	Biochemistry (General Principles)	Phenylketonuria
Subject	System	Topic

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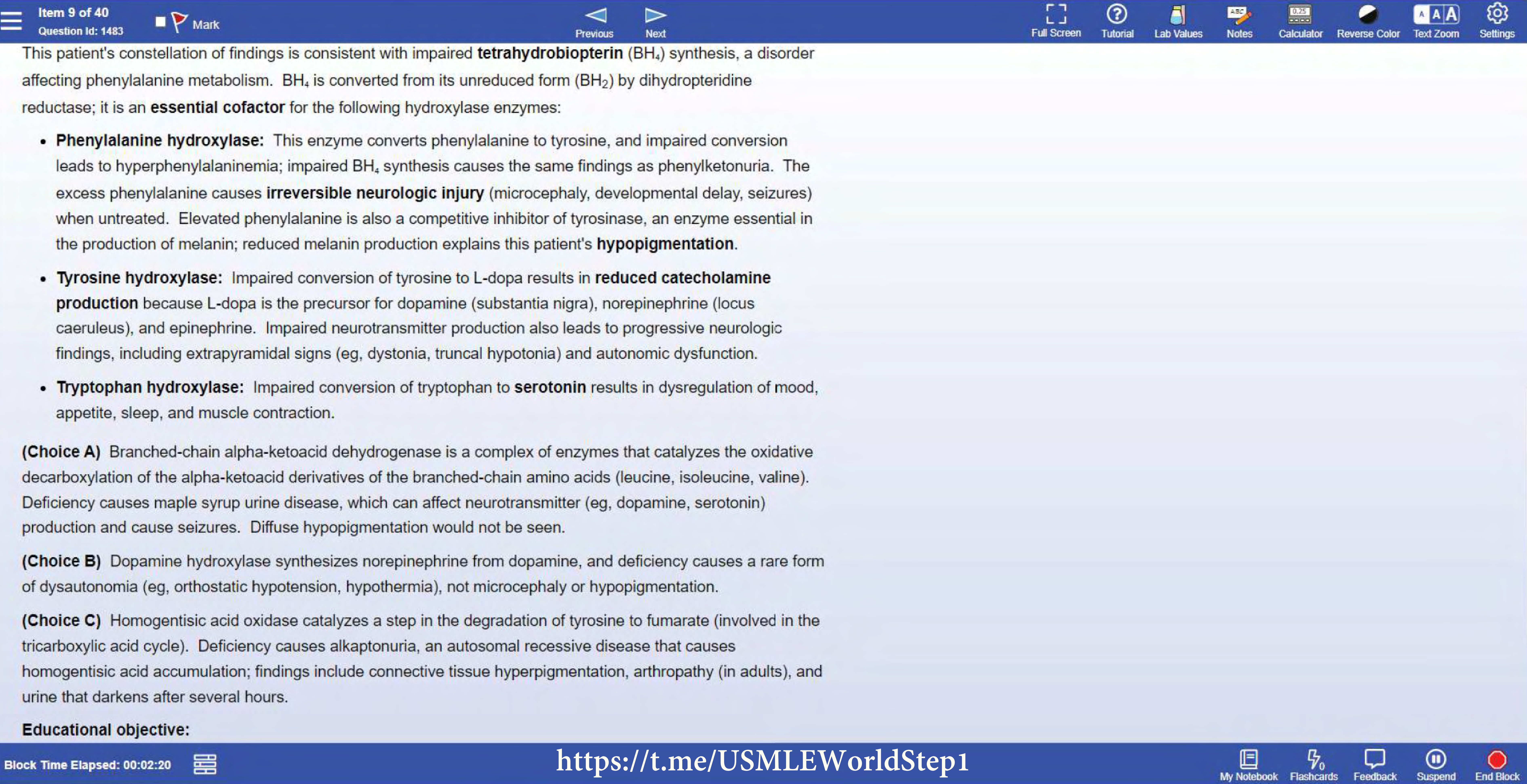

This patient's constellation of findings is consistent with impaired **tetrahydrobiopterin** (BH_4) synthesis, a disorder affecting phenylalanine metabolism. BH_4 is converted from its unreduced form (BH_2) by dihydropteridine reductase; it is an **essential cofactor** for the following hydroxylase enzymes:

- **Phenylalanine hydroxylase:** This enzyme converts phenylalanine to tyrosine, and impaired conversion leads to hyperphenylalaninemia; impaired BH_4 synthesis causes the same findings as phenylketonuria. The excess phenylalanine causes **irreversible neurologic injury** (microcephaly, developmental delay, seizures) when untreated. Elevated phenylalanine is also a competitive inhibitor of tyrosinase, an enzyme essential in the production of melanin; reduced melanin production explains this patient's **hypopigmentation**.
- **Tyrosine hydroxylase:** Impaired conversion of tyrosine to L-dopa results in **reduced catecholamine production** because L-dopa is the precursor for dopamine (substantia nigra), norepinephrine (locus caeruleus), and epinephrine. Impaired neurotransmitter production also leads to progressive neurologic findings, including extrapyramidal signs (eg, dystonia, truncal hypotonia) and autonomic dysfunction.
- **Tryptophan hydroxylase:** Impaired conversion of tryptophan to **serotonin** results in dysregulation of mood, appetite, sleep, and muscle contraction.

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Educational objective:

Block Time Elapsed: 00:02:20

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Correct answer
D

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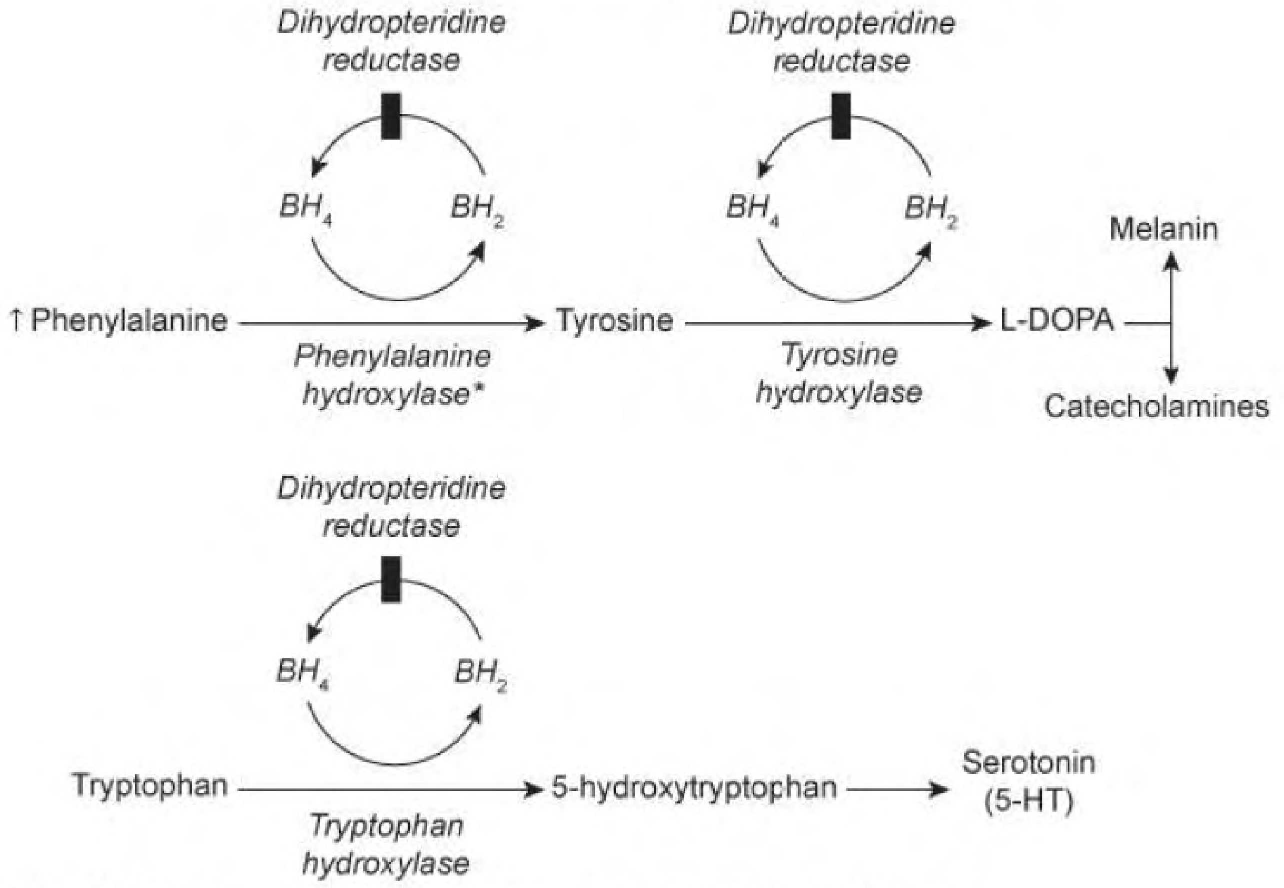
Impaired tetrahydrobiopterin (BH_4) synthesis


Dihydropteridine reductase
BH4
BH2
↑ Phenylalanine
Phenylalanine hydroxylase*
Tyrosine
Dihydropteridine reductase
BH4
BH2
Tyrosine hydroxylase
L-DOPA
Melanin
Catecholamines
Dihydropteridine reductase
BH4
BH2
Tryptophan
Tryptophan hydroxylase
5-hydroxytryptophan
Serotonin (5-HT)

*Phenylalanine hydroxylase deficiency results in phenylketonuria, another disorder of phenylalanine metabolism.

BH_2 = Dihydrobiopterin; **BH_4** = Tetrahydrobiopterin; **L-DOPA** = Levodopa

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reduct

- **Phenylalanine hydroxylase:** This enzyme converts phenylalanine to tyrosine, and impaired conversion

An autopsy is performed on a 9-month-old boy who died due to refractory seizures. The patient's family had recently immigrated to the United States, and he had a history of severe developmental delay and seizures. Examination shows microcephaly and skin with diffuse hypopigmentation. Further work-up reveals deficiency of a cofactor required for the formation of neurotransmitters found predominantly in the substantia nigra and locus caeruleus. The absence of this cofactor is most likely to directly affect the function of which of the following enzymes?

○ A. Branched-chain alpha-ketoacid dehydrogenase
✗ ● B. Dopamine hydroxylase
○ C. Homogentisic acid oxidase
✓ ○ D. Phenylalanine hydroxylase

Incorrect
Correct answer
D

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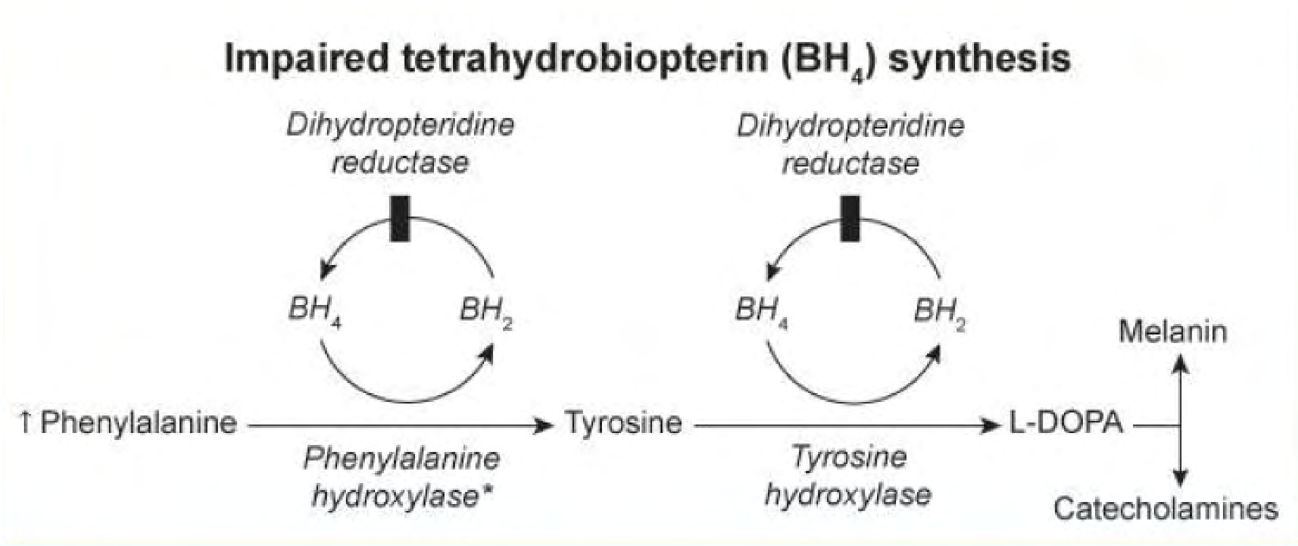
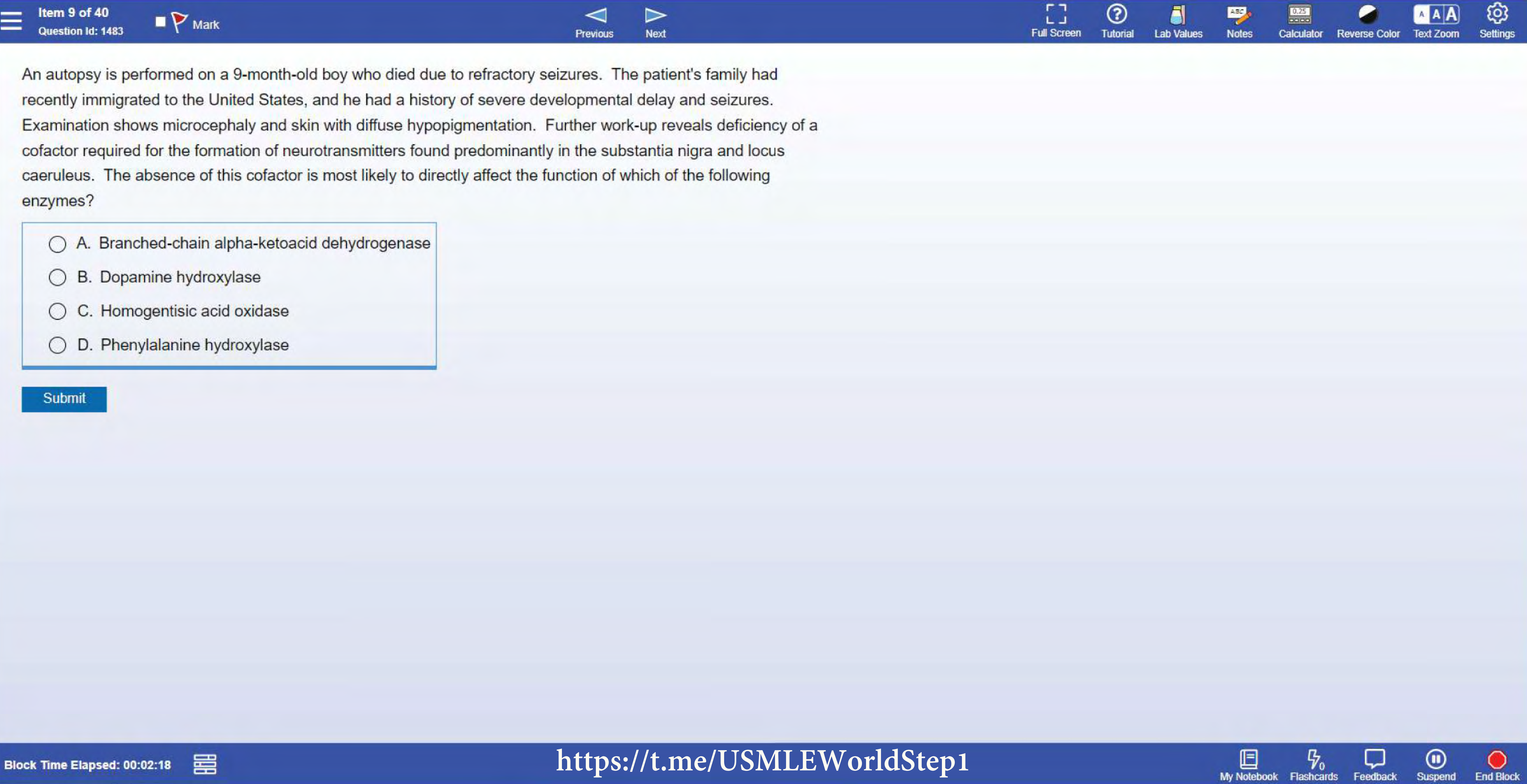
2023
Version

Explanation


Impaired tetrahydrobiopterin (BH4) synthesis
Dihydropteridine reductase
Dihydropteridine reductase
BH4
BH2
BH4
BH2
Melanin
↑ Phenylalanine
Tyrosine
L-DOPA
Phenylalanine hydroxylase*
Tyrosine hydroxylase
Catecholamines


Item 9 of 40
Question Id: 1483
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:02:18
My Notebook
Flashcards
Feedback
Suspend
End Block

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- ○ B. Dopamine hydroxylase
- ○ C. Homogentisic acid oxidase
- ○ D. Phenylalanine hydroxylase

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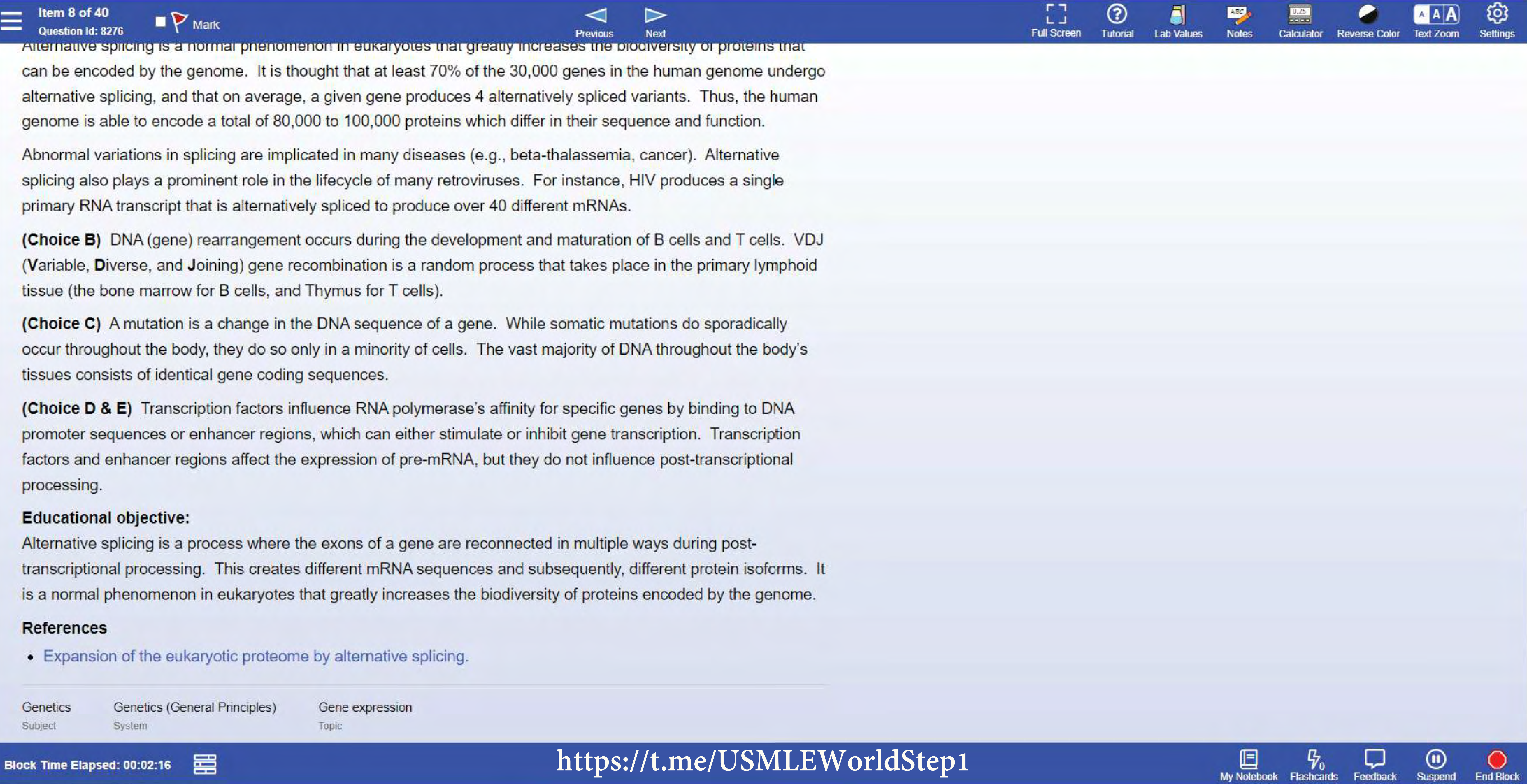


Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that can be encoded by the genome. It is thought that at least 70% of the 30,000 genes in the human genome undergo alternative splicing, and that on average, a given gene produces 4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

Abnormal variations in splicing are implicated in many diseases (e.g., beta-thalassemia, cancer). Alternative splicing also plays a prominent role in the lifecycle of many retroviruses. For instance, HIV produces a single primary RNA transcript that is alternatively spliced to produce over 40 different mRNAs.

(Choice B) DNA (gene) rearrangement occurs during the development and maturation of B cells and T cells. VDJ (**V**ariable, **D**iverse, and **J**oining) gene recombination is a random process that takes place in the primary lymphoid tissue (the bone marrow for B cells, and Thymus for T cells).

(Choice C) A mutation is a change in the DNA sequence of a gene. While somatic mutations do sporadically occur throughout the body, they do so only in a minority of cells. The vast majority of DNA throughout the body's tissues consists of identical gene coding sequences.

(Choice D & E) Transcription factors influence RNA polymerase's affinity for specific genes by binding to DNA promoter sequences or enhancer regions, which can either stimulate or inhibit gene transcription. Transcription factors and enhancer regions affect the expression of pre-mRNA, but they do not influence post-transcriptional processing.

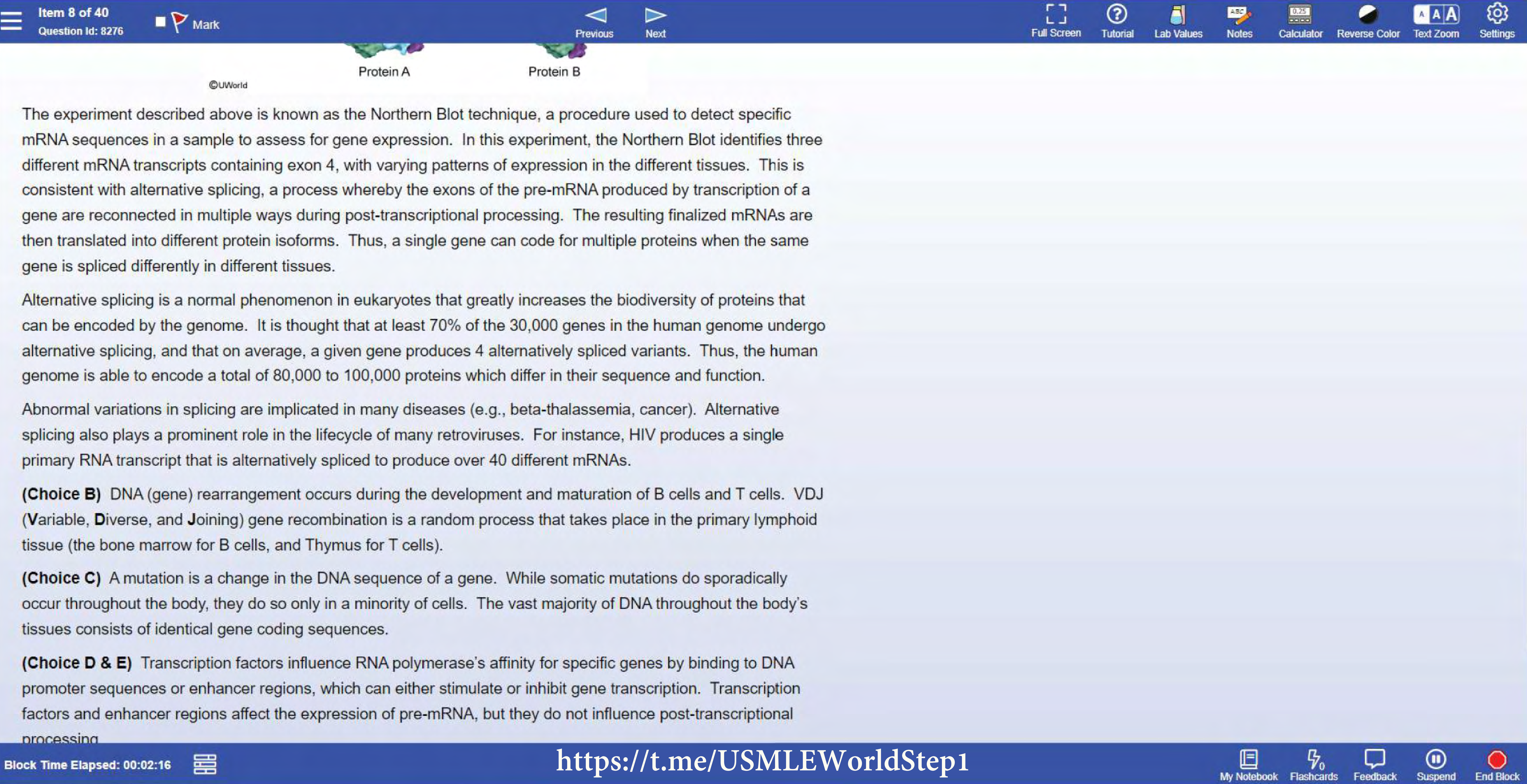
Educational objective:

Alternative splicing is a process where the exons of a gene are reconnected in multiple ways during post-transcriptional processing. This creates different mRNA sequences and subsequently, different protein isoforms. It is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins encoded by the genome.

References

- Expansion of the eukaryotic proteome by alternative splicing.

Genetics	Genetics (General Principles)	Gene expression
Subject	System	Topic



The experiment described above is known as the Northern Blot technique, a procedure used to detect specific mRNA sequences in a sample to assess for gene expression. In this experiment, the Northern Blot identifies three different mRNA transcripts containing exon 4, with varying patterns of expression in the different tissues. This is consistent with alternative splicing, a process whereby the exons of the pre-mRNA produced by transcription of a gene are reconnected in multiple ways during post-transcriptional processing. The resulting finalized mRNAs are then translated into different protein isoforms. Thus, a single gene can code for multiple proteins when the same gene is spliced differently in different tissues.

Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that can be encoded by the genome. It is thought that at least 70% of the 30,000 genes in the human genome undergo alternative splicing, and that on average, a given gene produces 4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

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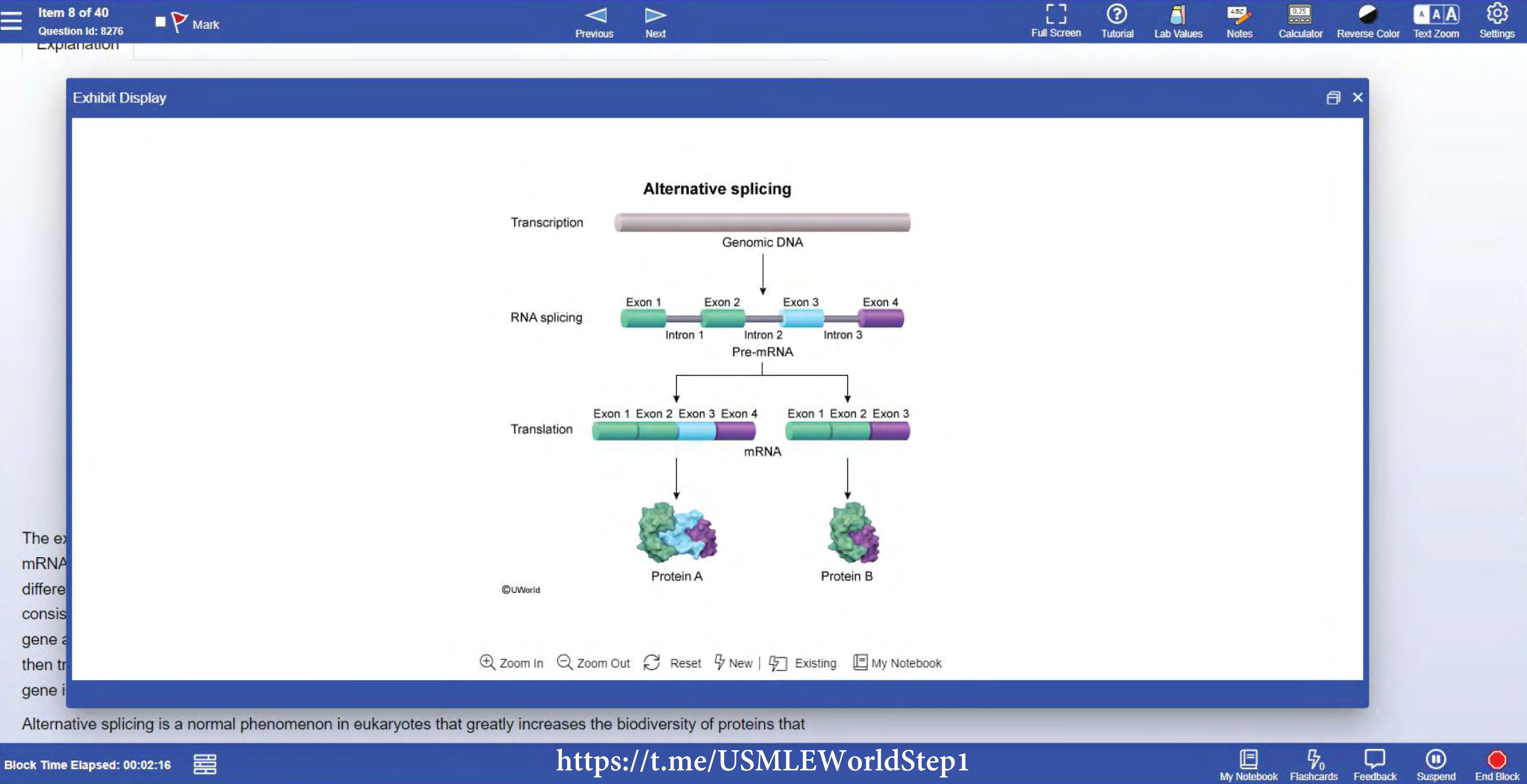
Item 8 of 40
Question Id: 8276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Exhibit Display
Alternative splicing
Transcription
Genomic DNA
RNA splicing
Exon 1
Exon 2
Exon 3
Exon 4
Intron 1
Intron 2
Intron 3
Pre-mRNA
Translation
Exon 1 Exon 2 Exon 3 Exon 4
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My Notebook
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Flashcards
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Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that

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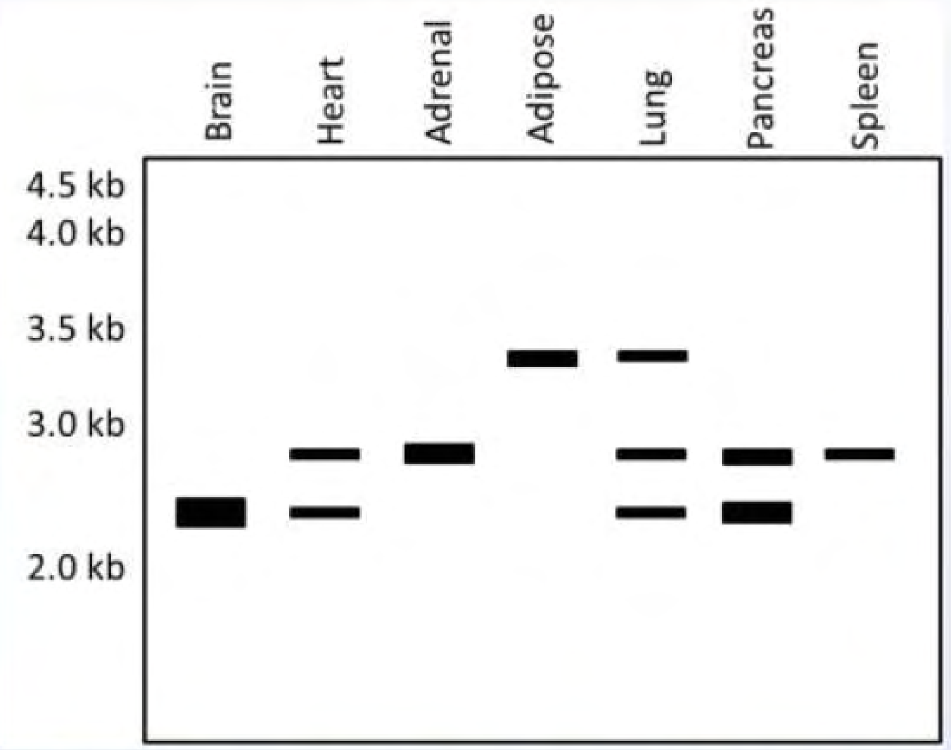
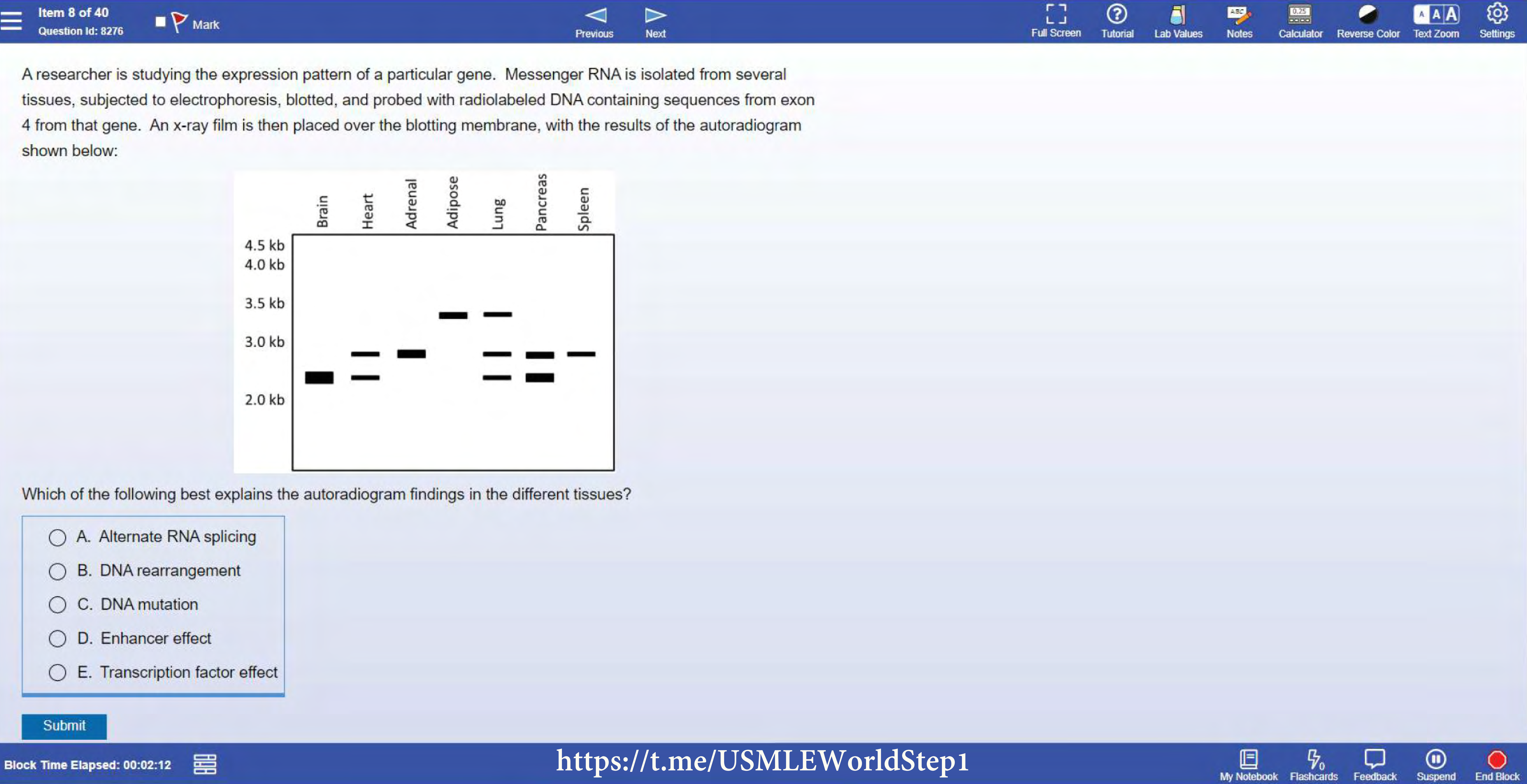
A researcher is studying the expression pattern of a particular gene. Messenger RNA is isolated from several tissues, subjected to electrophoresis, blotted, and probed with radiolabeled DNA containing sequences from exon 4 from that gene. An x-ray film is then placed over the blotting membrane, with the results of the autoradiogram shown below:



Which of the following best explains the autoradiogram findings in the different tissues?

- ✓ ● A. Alternate RNA splicing (78%)
- ○ B. DNA rearrangement (4%)
- ○ C. DNA mutation (2%)
- ○ D. Enhancer effect (4%)
- ○ E. Transcription factor effect (10%)

Correct 78% 04 secs 2023


Item 8 of 40
Question Id: 8276
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Brain
Heart
Adrenal
Adipose
Lung
Pancreas
Spleen
4.5 kb
4.0 kb
3.5 kb
3.0 kb
2.0 kb

Which of the following best explains the autoradiogram findings in the different tissues?

○ A. Alternate RNA splicing

○ B. DNA rearrangement

○ C. DNA mutation

○ D. Enhancer effect

○ E. Transcription factor effect

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Block Time Elapsed: 00:02:12
My Notebook
Flashcards
Feedback
Suspend
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nucleolus. **RNA polymerase I** functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene into a single transcript that is subsequently processed into mature 18S, 5.8S, and 28S rRNAs.

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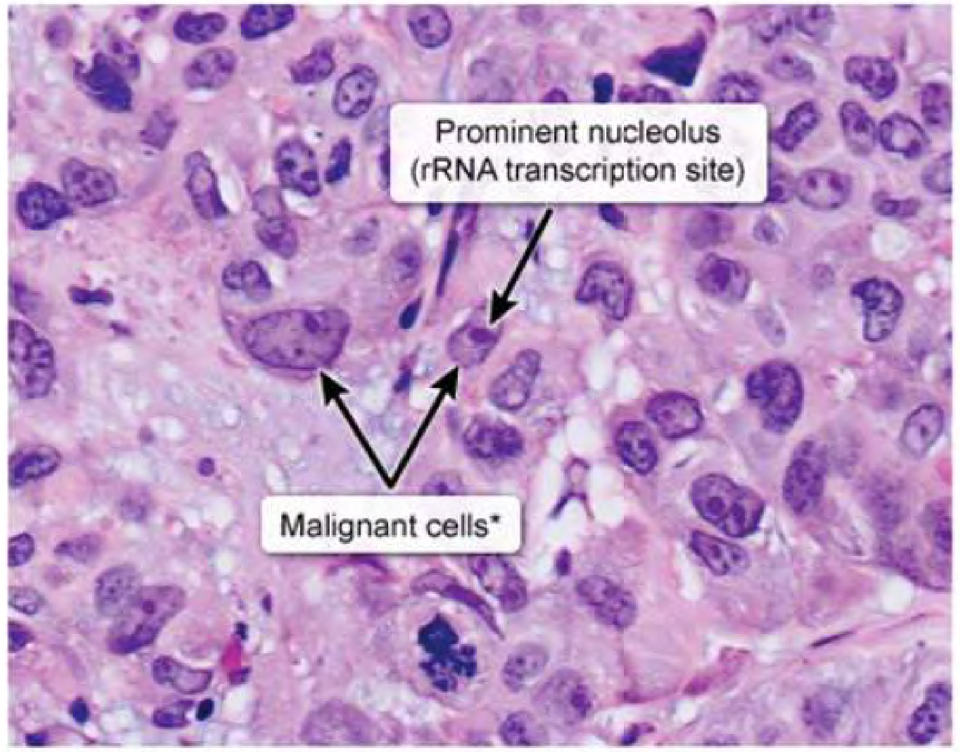

*Pleomorphic cells with large, irregular nuclei and prominent nucleoli.
rRNA = ribosomal RNA.

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nucleolus. **RNA polymerase I** functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene into a single transcript that is subsequently processed into mature 18S, 5.8S, and 28S rRNAs.

In addition to rRNA transcription, the nucleolus is involved in the maturation and **assembly of ribosomal subunits**. Ribosomal proteins, which are synthesized in the cytoplasm, are transported into the nucleolus, where they combine with rRNA to form immature 40S and 60S subunits. These subunits are then shuttled via nuclear pores to the cytoplasm, where they ultimately participate in protein synthesis.

The regulation of ribosomal synthesis occurs in part by controlling the number of active rRNA genes. Generally, as cells become more differentiated, growth slows and the cells require fewer ribosomes for protein production. In contrast, **malignant cells** with high metabolic activity usually have a large number of active rRNA genes and prominent nucleoli.

(Choice A) Peptidyltransferase catalyzes peptide bond formation during protein synthesis, which occurs in mature ribosomes found in the cytoplasm.

(Choice C) RNA polymerase II synthesizes messenger RNA (mRNA), small nuclear RNA (snRNA), and microRNA (miRNA) in the nucleus. It is the most highly regulated of the 3 RNA polymerases, with its function determined by multiple transcription factors and epigenetic processes.

(Choice D) Ubiquitin ligase attaches ubiquitin molecules to proteins in the cytoplasm, tagging them for degradation in the cell's proteasome complex. The ubiquitin-proteasome pathway is important for the degradation of short-lived, senescent, or abnormal (eg, denatured, misfolded) proteins.

Educational objective:
The nucleolus is the site of ribosomal RNA (rRNA) transcription and ribosomal subunit assembly. RNA polymerase I functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene, which codes for most of the rRNA components (18S, 5.8S, and 28S rRNAs).

Genetics	Genetics (General Principles)	Protein synthesis
Subject	System	Topic

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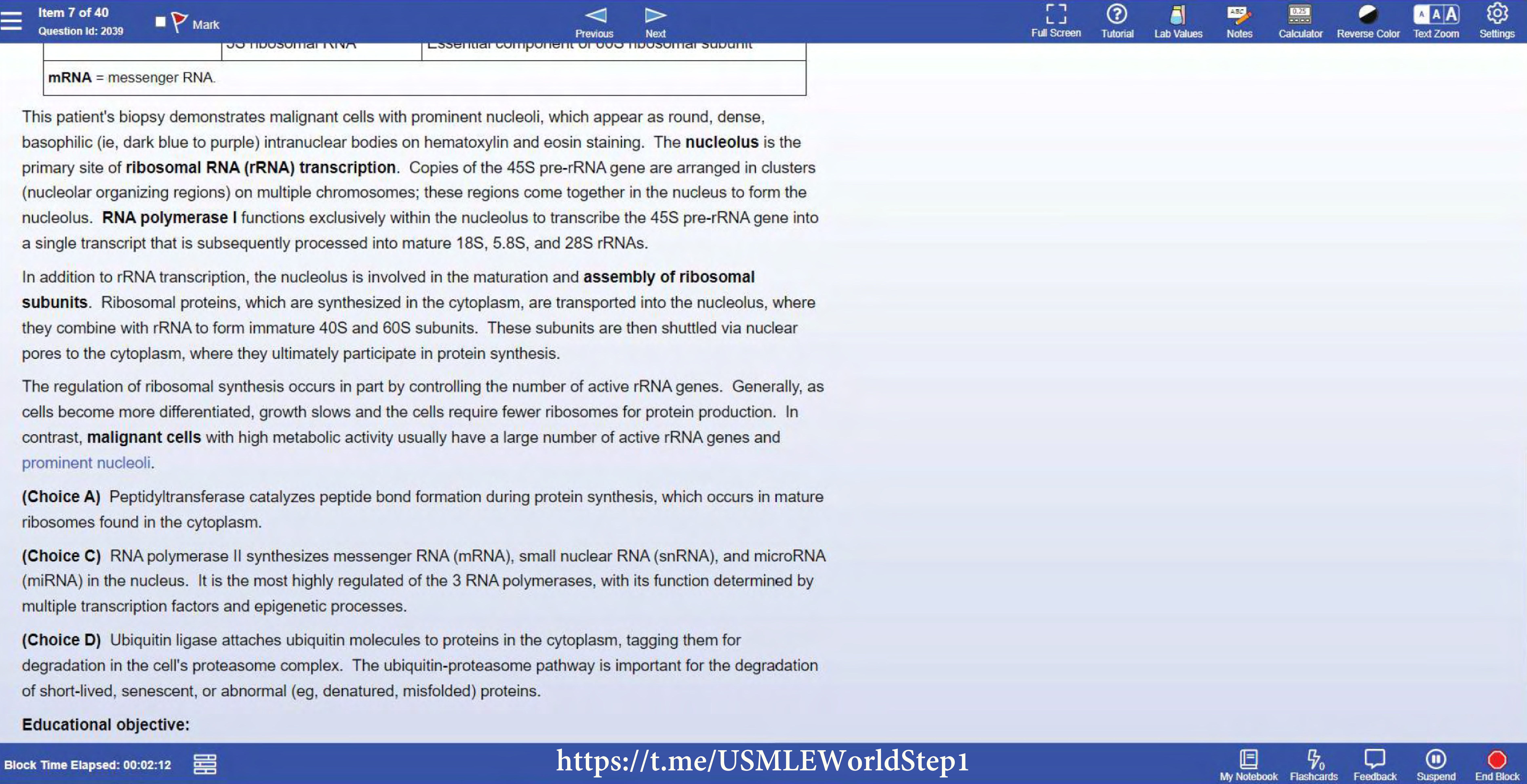

	5S ribosomal RNA	Essential component of 60S ribosomal subunit
mRNA = messenger RNA.		

This patient's biopsy demonstrates malignant cells with prominent nucleoli, which appear as round, dense, basophilic (ie, dark blue to purple) intranuclear bodies on hematoxylin and eosin staining. The **nucleolus** is the primary site of **ribosomal RNA (rRNA) transcription**. Copies of the 45S pre-rRNA gene are arranged in clusters (nucleolar organizing regions) on multiple chromosomes; these regions come together in the nucleus to form the nucleolus. **RNA polymerase I** functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene into a single transcript that is subsequently processed into mature 18S, 5.8S, and 28S rRNAs.

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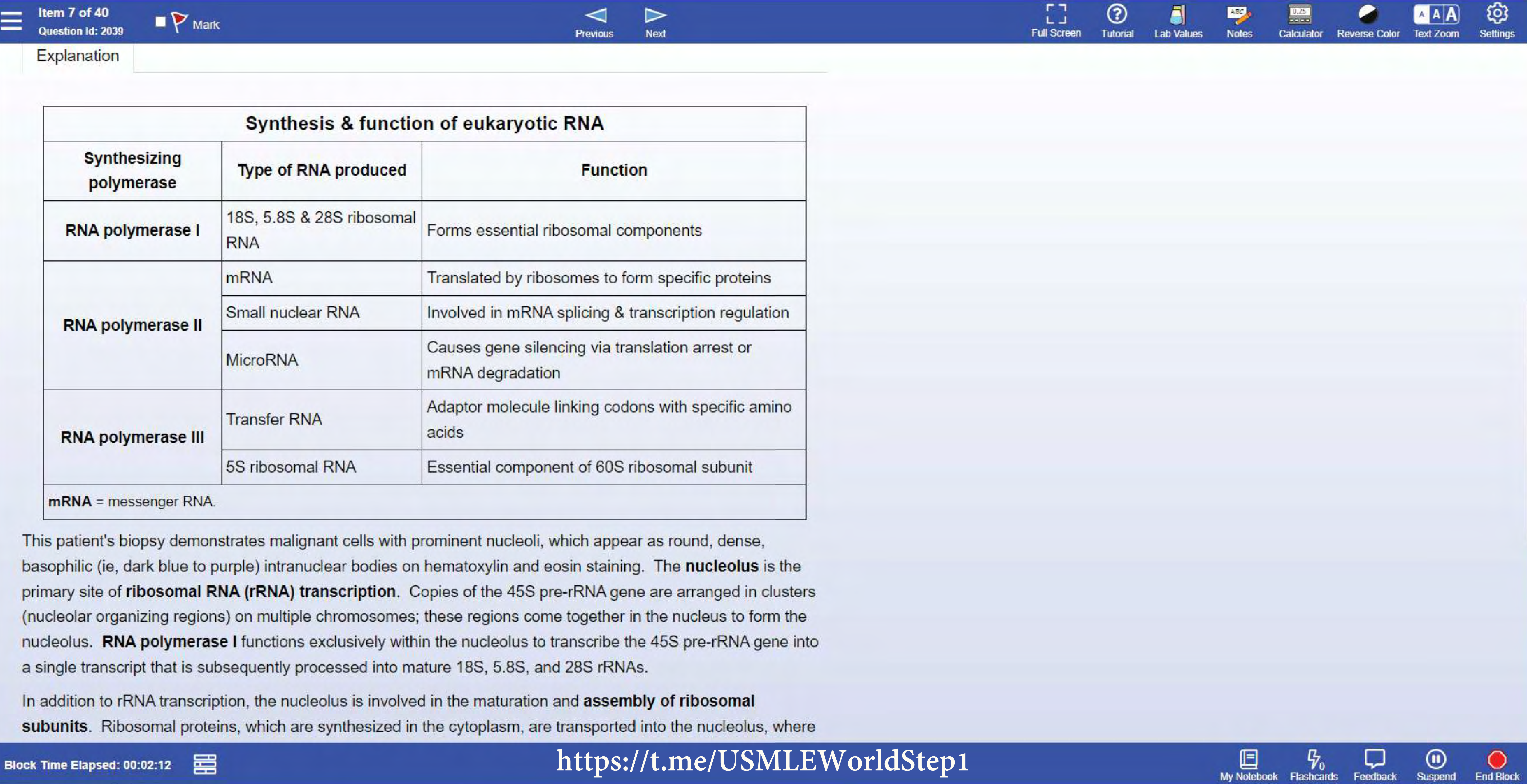
Educational objective:


Item 7 of 40
Question Id: 2039
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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My Notebook
Flashcards
Feedback
Suspend
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Explanation

Synthesis & function of eukaryotic RNA

Synthesizing polymerase	Type of RNA produced	Function
RNA polymerase I	18S, 5.8S & 28S ribosomal RNA	Forms essential ribosomal components
RNA polymerase II	mRNA	Translated by ribosomes to form specific proteins
	Small nuclear RNA	Involved in mRNA splicing & transcription regulation
	MicroRNA	Causes gene silencing via translation arrest or mRNA degradation
RNA polymerase III	Transfer RNA	Adaptor molecule linking codons with specific amino acids
	5S ribosomal RNA	Essential component of 60S ribosomal subunit

mRNA = messenger RNA.

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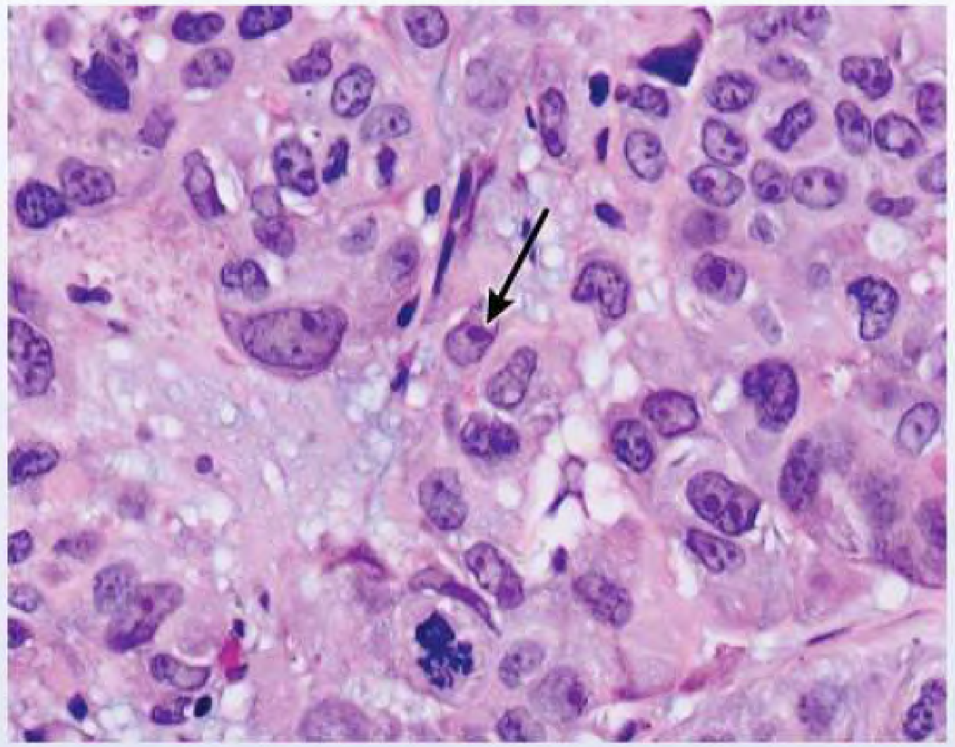
A 58-year-old man comes to the office with a persistent dry cough. He also has involuntarily lost 10 kg (22 lb) over the past 3 months. The patient drinks 2 or 3 beers daily and has a 40-pack-year smoking history. Physical examination shows dullness to percussion over the right lower lung base. CT scan of the chest reveals a right-sided pleural effusion and a mass in the lower lobe of the right lung. Microscopic examination of the mass demonstrates malignant cells with large nuclei that contain prominent, round, basophilic bodies, as shown in the image below:



Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

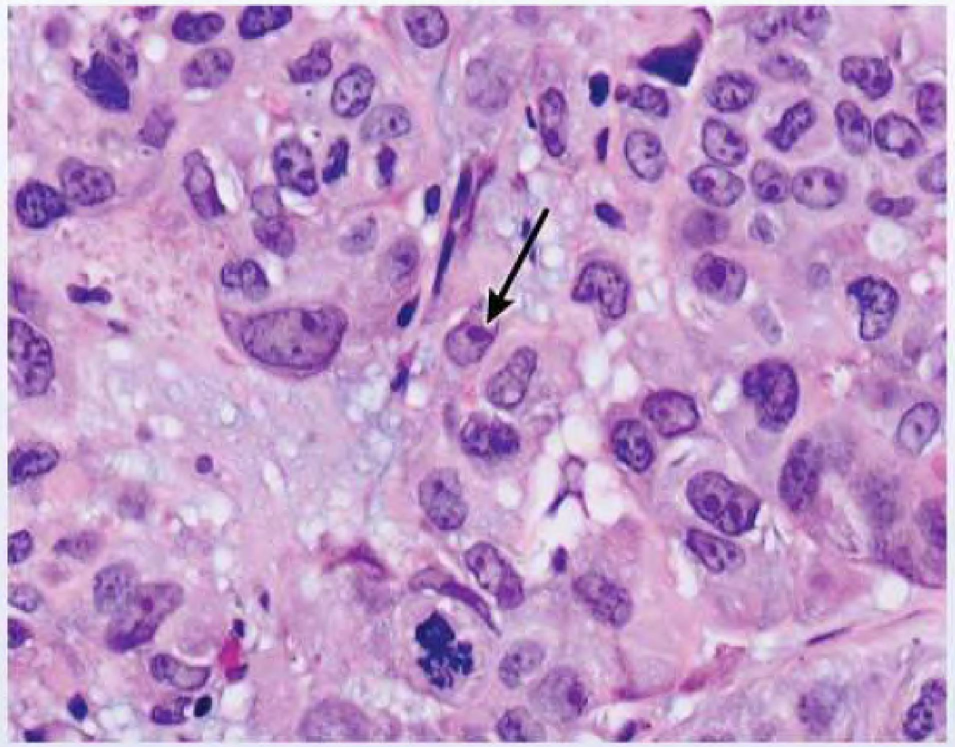
○ A. Peptidyltransferase (10%)

✓ ● B. RNA polymerase I (45%)

○ C. RNA polymerase II (27%)

○ D. Ubiquitin ligase (16%)

A 58-year-old man comes to the office with a persistent dry cough. He also has involuntarily lost 10 kg (22 lb) over the past 3 months. The patient drinks 2 or 3 beers daily and has a 40-pack-year smoking history. Physical examination shows dullness to percussion over the right lower lung base. CT scan of the chest reveals a right-sided pleural effusion and a mass in the lower lobe of the right lung. Microscopic examination of the mass demonstrates malignant cells with large nuclei that contain prominent, round, basophilic bodies, as shown in the image below:



Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

○ A. Peptidyltransferase
○ B. RNA polymerase I
○ C. RNA polymerase II
○ D. Ubiquitin ligase

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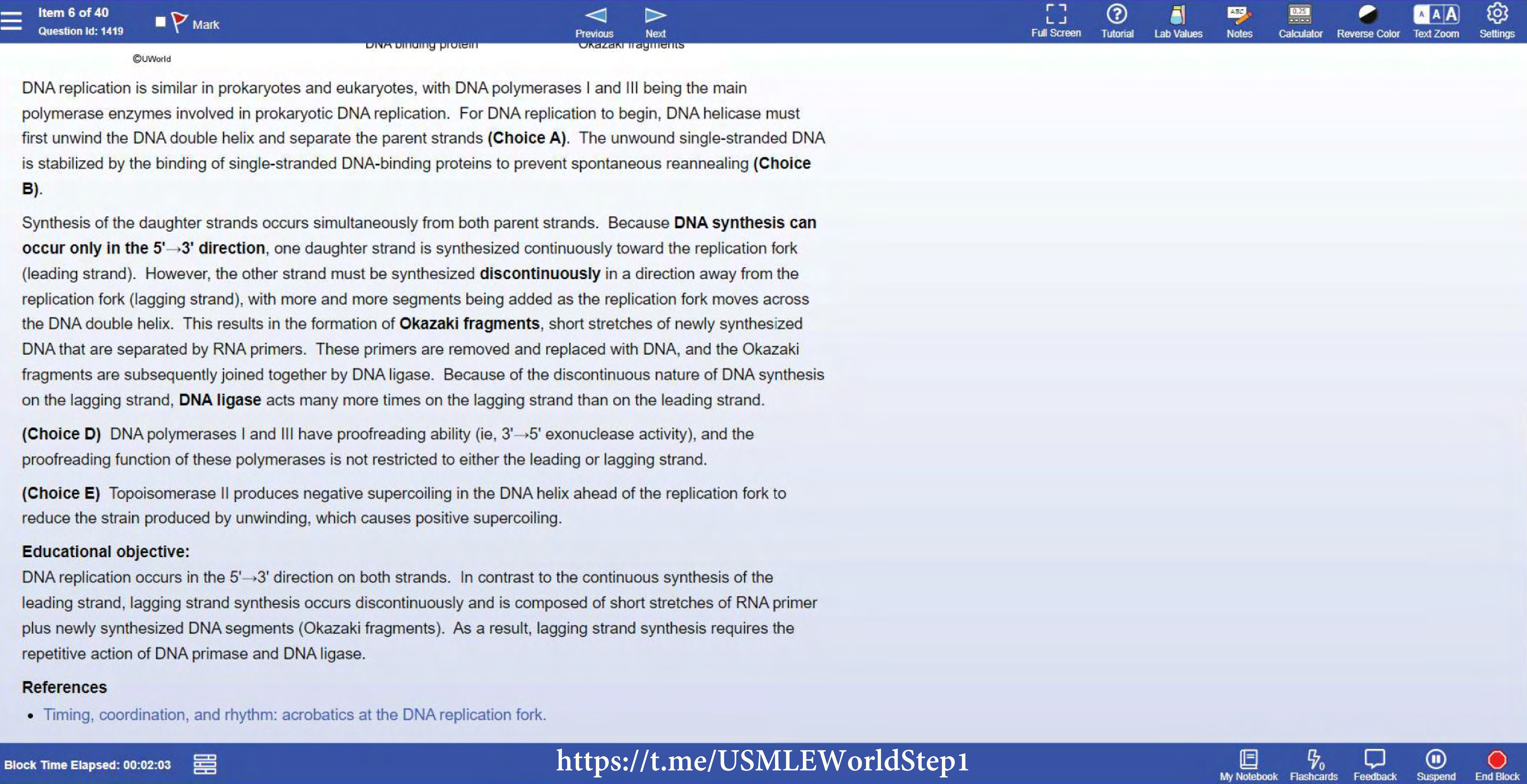
Item 6 of 40
Question Id: 1419
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
DNA binding protein
Okazaki fragments
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My Notebook
Flashcards
Feedback
Suspend
End Block

DNA replication is similar in prokaryotes and eukaryotes, with DNA polymerases I and III being the main polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands **(Choice A)**. The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous reannealing **(Choice B)**.

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized continuously toward the replication fork (leading strand). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (lagging strand), with more and more segments being added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase. Because of the discontinuous nature of DNA synthesis on the lagging strand, **DNA ligase** acts many more times on the lagging strand than on the leading strand.

(Choice D) DNA polymerases I and III have proofreading ability (ie, 3'→5' exonuclease activity), and the proofreading function of these polymerases is not restricted to either the leading or lagging strand.

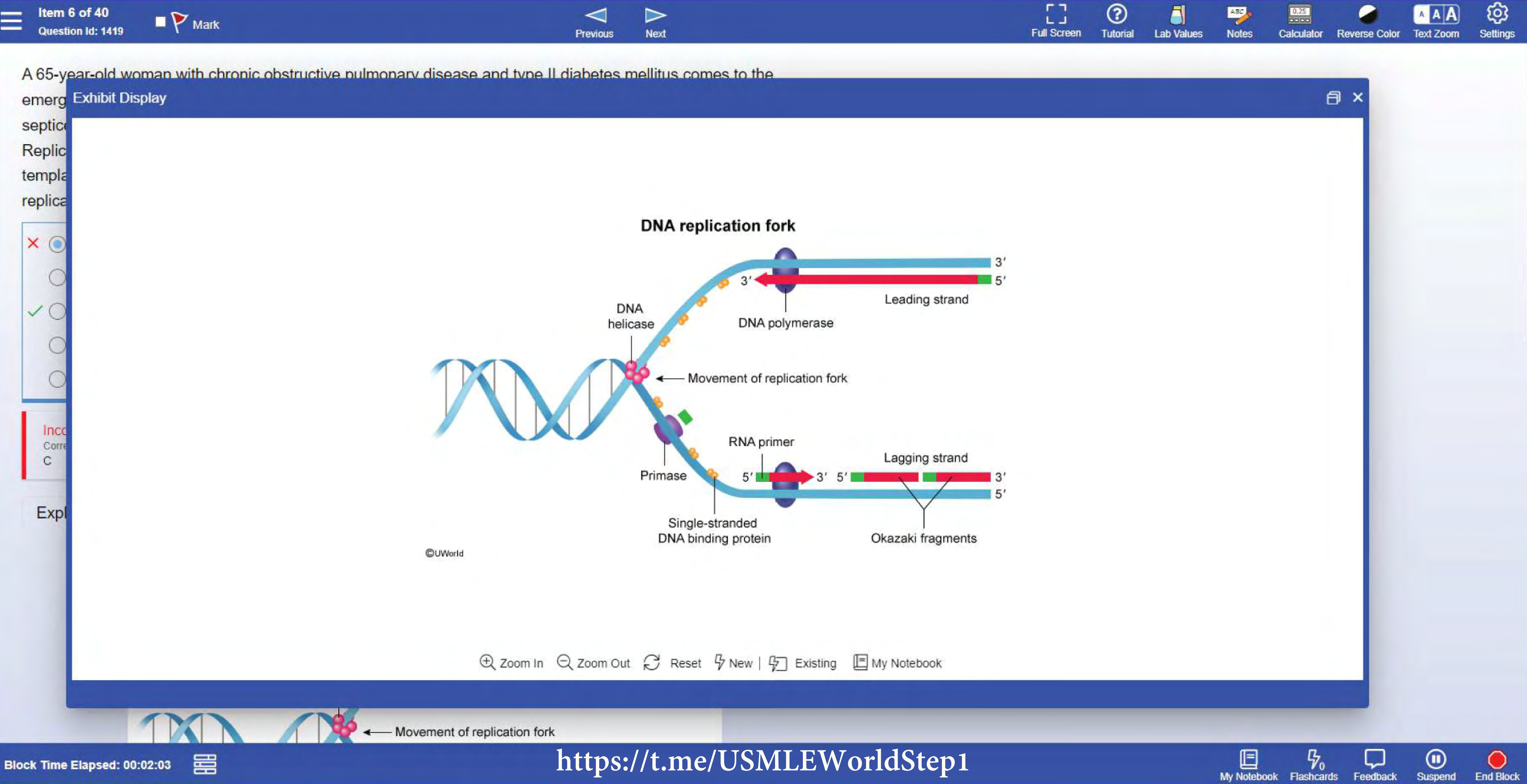
(Choice E) Topoisomerase II produces negative supercoiling in the DNA helix ahead of the replication fork to reduce the strain produced by unwinding, which causes positive supercoiling.

Educational objective:

DNA replication occurs in the 5'→3' direction on both strands. In contrast to the continuous synthesis of the leading strand, lagging strand synthesis occurs discontinuously and is composed of short stretches of RNA primer plus newly synthesized DNA segments (Okazaki fragments). As a result, lagging strand synthesis requires the repetitive action of DNA primase and DNA ligase.

References

- Timing, coordination, and rhythm: acrobatics at the DNA replication fork.


Item 6 of 40
Question Id: 1419
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
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DNA replication fork
3′
5′
3′
Leading strand
DNA polymerase
DNA helicase
Movement of replication fork
RNA primer
Lagging strand
Primase
5′
3′
5′
3′
5′
Single-stranded DNA binding protein
Okazaki fragments
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A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the

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A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

- ✗ ● A. Enzymatic function of DNA helicase (2%)
- ○ B. Interaction with single-stranded DNA-binding proteins (8%)
- ✓ ○ C. Joining of DNA fragments by ligase (65%)
- ○ D. Proofreading of the newly synthesized DNA (19%)
- ○ E. Relief of supercoils by topoisomerase (3%)

Incorrect
Correct answer
C

65%
Answered correctly

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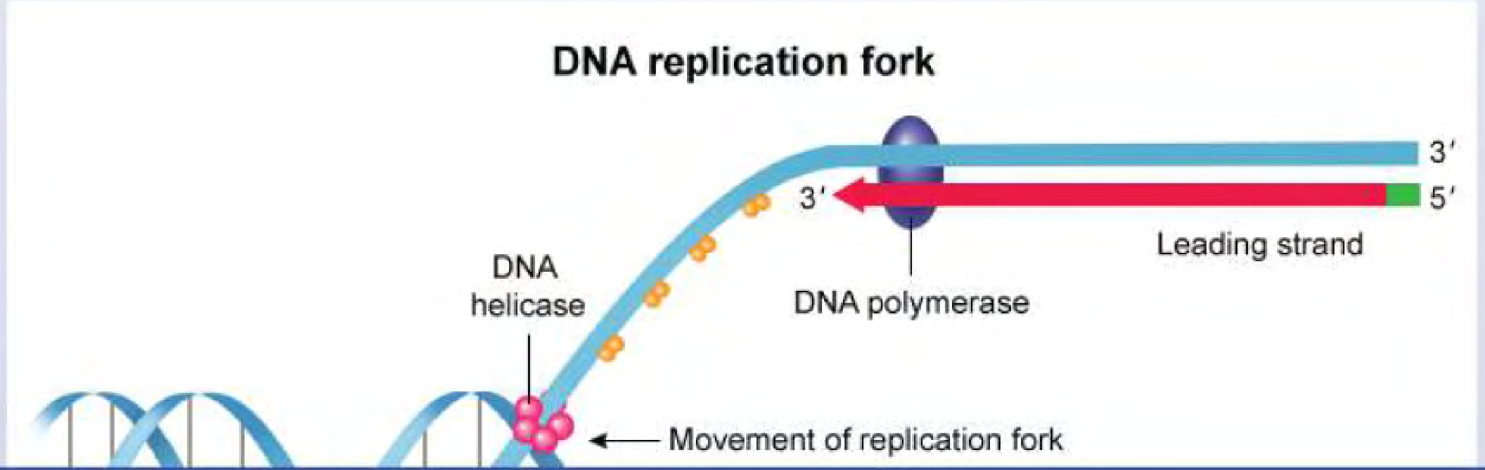
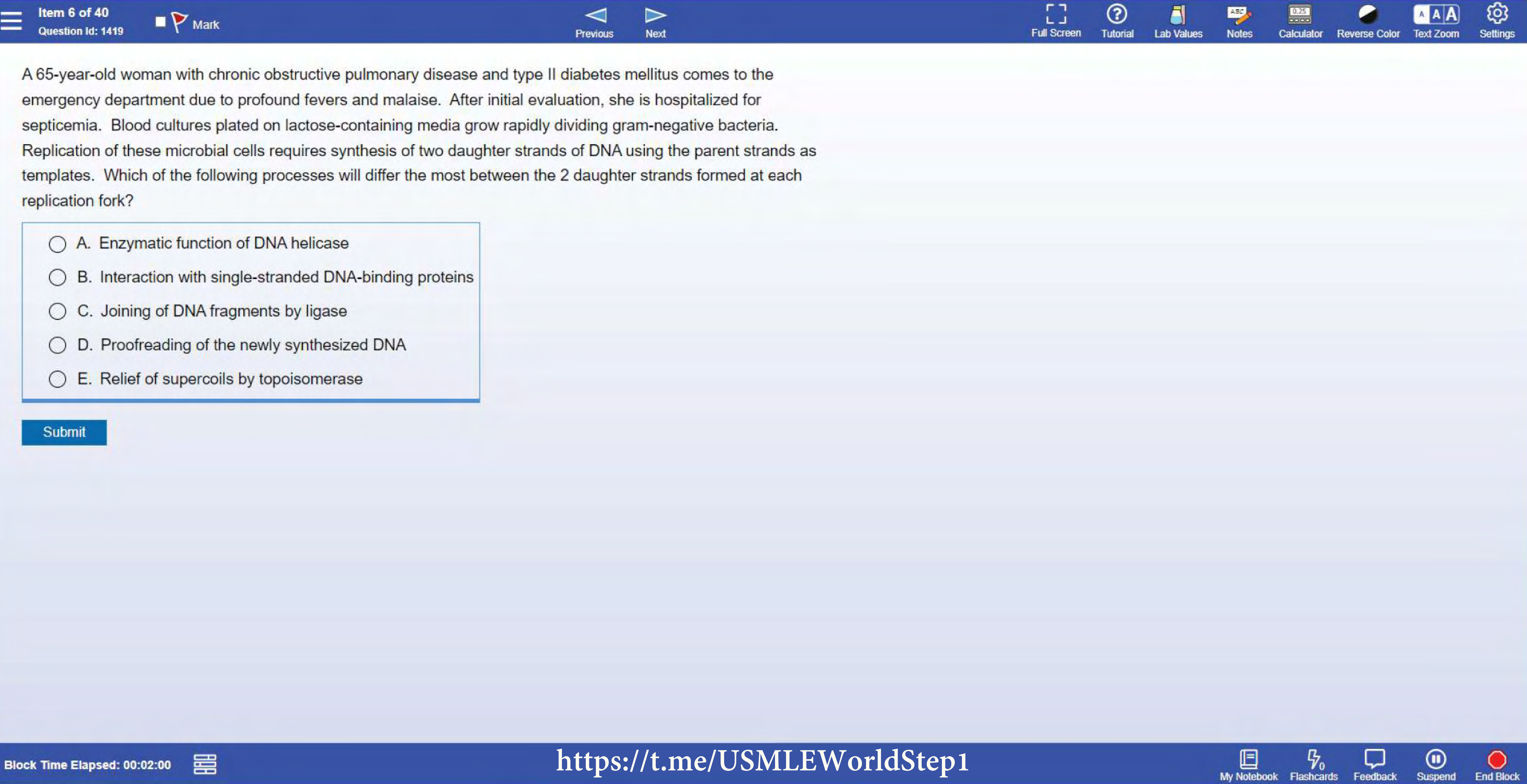
Explanation




Item 6 of 40
Question Id: 1419
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ D. Proofreading of the newly synthesized DNA
○ E. Relief of supercoils by topoisomerase

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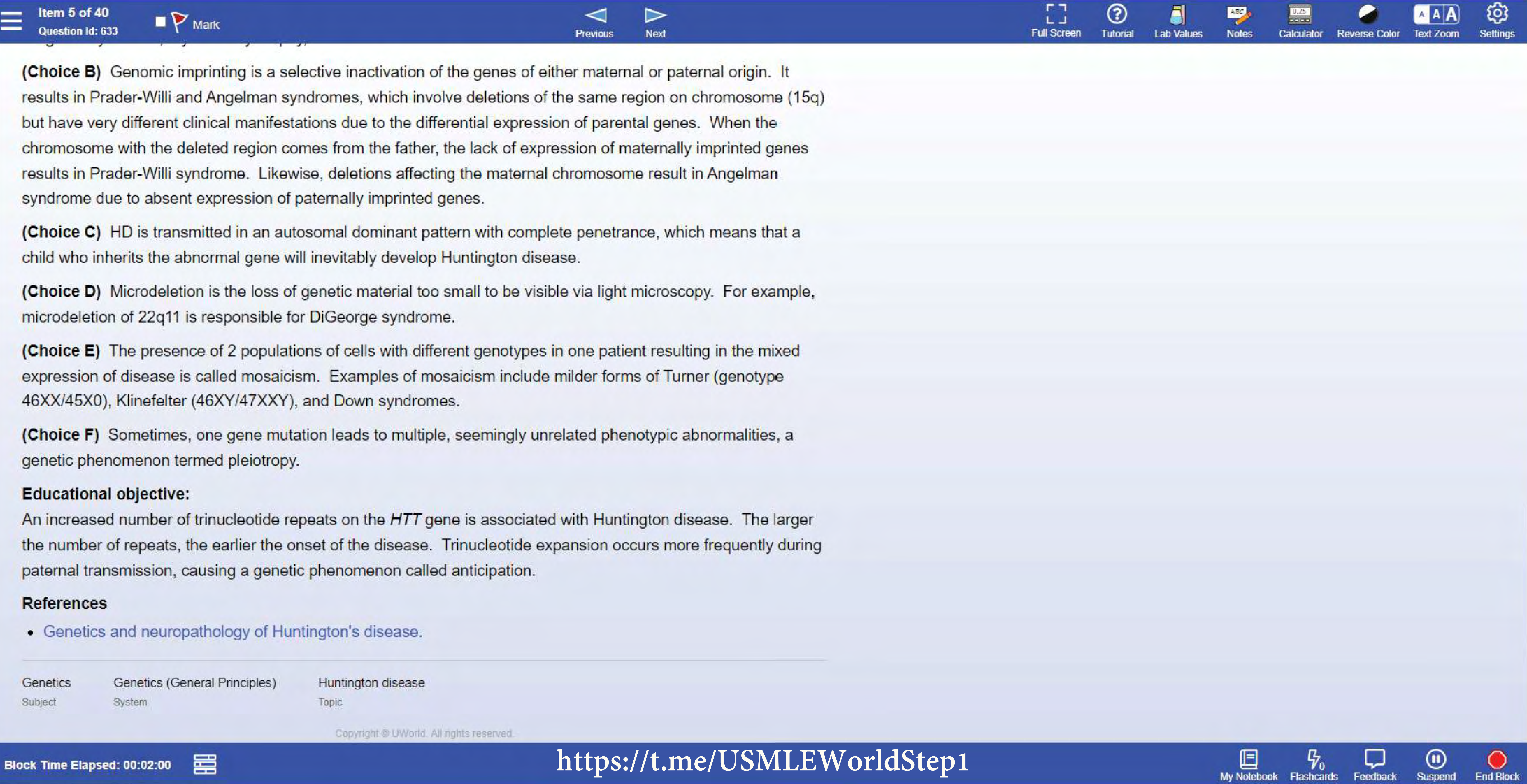

Item 5 of 40
Question Id: 633

(Choice B) Genomic imprinting is a selective inactivation of the genes of either maternal or paternal origin. It results in Prader-Willi and Angelman syndromes, which involve deletions of the same region on chromosome (15q) but have very different clinical manifestations due to the differential expression of parental genes. When the chromosome with the deleted region comes from the father, the lack of expression of maternally imprinted genes results in Prader-Willi syndrome. Likewise, deletions affecting the maternal chromosome result in Angelman syndrome due to absent expression of paternally imprinted genes.

(Choice C) HD is transmitted in an autosomal dominant pattern with complete penetrance, which means that a child who inherits the abnormal gene will inevitably develop Huntington disease.

(Choice D) Microdeletion is the loss of genetic material too small to be visible via light microscopy. For example, microdeletion of 22q11 is responsible for DiGeorge syndrome.

(Choice E) The presence of 2 populations of cells with different genotypes in one patient resulting in the mixed expression of disease is called mosaicism. Examples of mosaicism include milder forms of Turner (genotype 46XX/45X0), Klinefelter (46XY/47XXY), and Down syndromes.

(Choice F) Sometimes, one gene mutation leads to multiple, seemingly unrelated phenotypic abnormalities, a genetic phenomenon termed pleiotropy.

Educational objective:

An increased number of trinucleotide repeats on the *HTT* gene is associated with Huntington disease. The larger the number of repeats, the earlier the onset of the disease. Trinucleotide expansion occurs more frequently during paternal transmission, causing a genetic phenomenon called anticipation.

References

- Genetics and neuropathology of Huntington's disease.

Genetics	Genetics (General Principles)	Huntington disease
Subject	System	Topic

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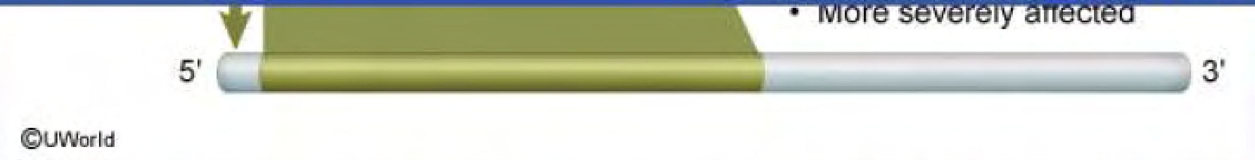

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This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely has **Huntington disease** (HD), which typically manifests with the triad of movement disorder (chorea), behavioral abnormalities (aggressiveness, apathy, or depression), and dementia. HD is caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats. Most patients develop symptoms in their 40s or 50s, but an earlier age of onset and more severe symptoms are associated with a larger number of **trinucleotide repeats**.

During spermatogenesis, CAG repeats in the abnormal *HTT* gene (chromosome 4p) can rapidly increase (much more than during oogenesis). Therefore, patients who receive an abnormal gene from their fathers tend to develop the disease earlier in life. The tendency for clinical symptoms to worsen and/or occur earlier in subsequent generations is called **anticipation**. Anticipation is common in disorders associated with trinucleotide repeats, as in Fragile X syndrome, myotonic dystrophy, and Friedreich ataxia.

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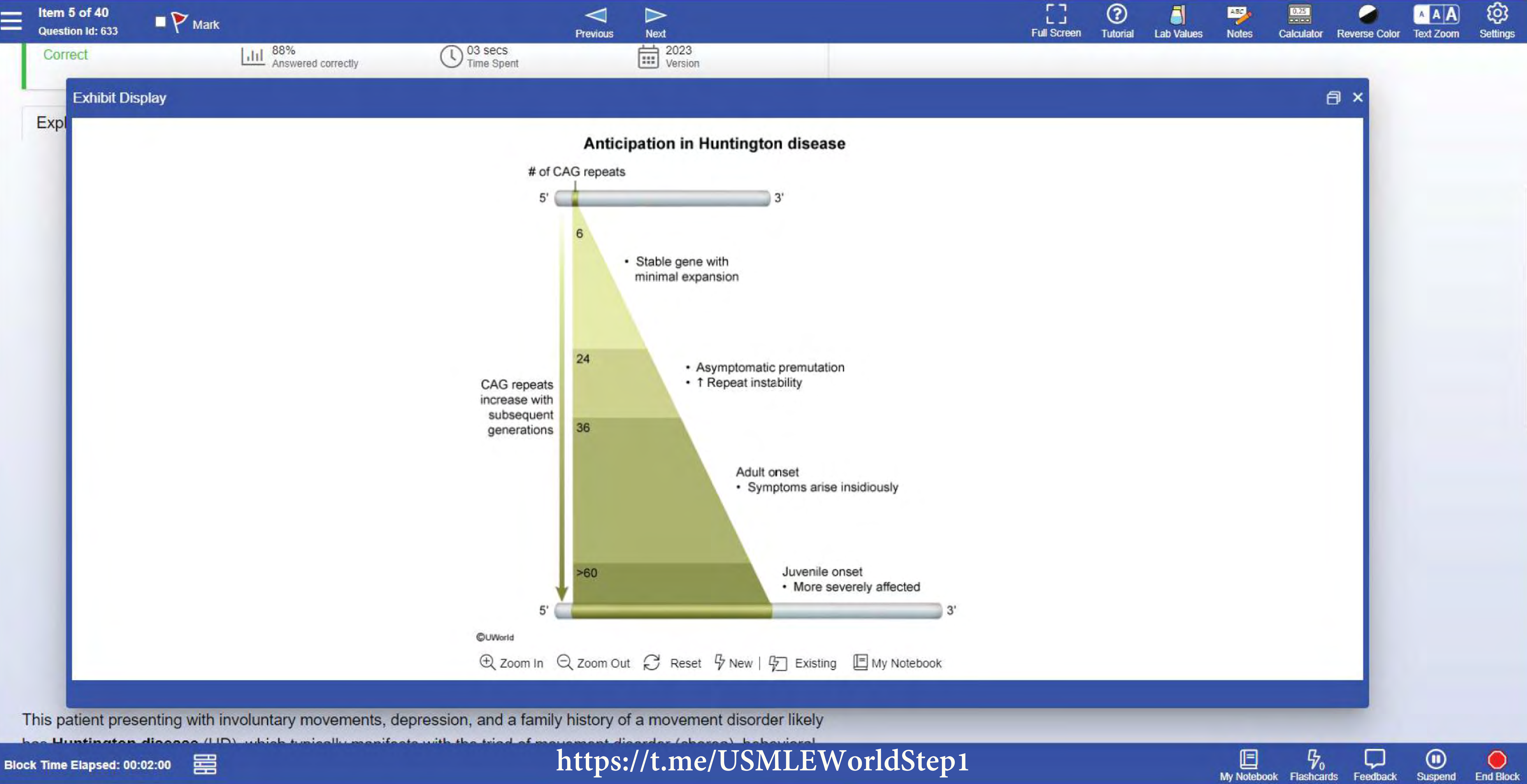
Item 5 of 40
Question Id: 633
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
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Correct
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Expl
Exhibit Display
Anticipation in Huntington disease
# of CAG repeats
5'
3'
6
• Stable gene with minimal expansion
24
• Asymptomatic premutation
• ↑ Repeat instability
CAG repeats increase with subsequent generations
36
Adult onset
• Symptoms arise insidiously
>60
Juvenile onset
• More severely affected
5'
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Feedback
Suspend
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This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely

A 28-year-old man is evaluated for abnormal movements of the hands and face. The patient reports that he started experiencing involuntary grimacing a year ago, which has gradually worsened. He is taking a selective serotonin reuptake inhibitor for major depression but has not taken any antipsychotic medications. His 52-year-old father was diagnosed with an inherited movement disorder 2 months ago. Physical examination shows normal strength and normal deep tendon reflexes. No sensory deficits are noted. Which of the following best explains the difference in disease presentation between this patient and his father?

- ✓ ● A. Anticipation (88%)
- ○ B. Genomic imprinting (0%)
- ○ C. Incomplete penetrance (5%)
- ○ D. Microdeletion (0%)
- ○ E. Mosaicism (1%)
- ○ F. Pleiotropy (2%)

Correct

88% Answered correctly

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2023 Version

Explanation

Anticipation in Huntington disease

# of CAG repeats
5'
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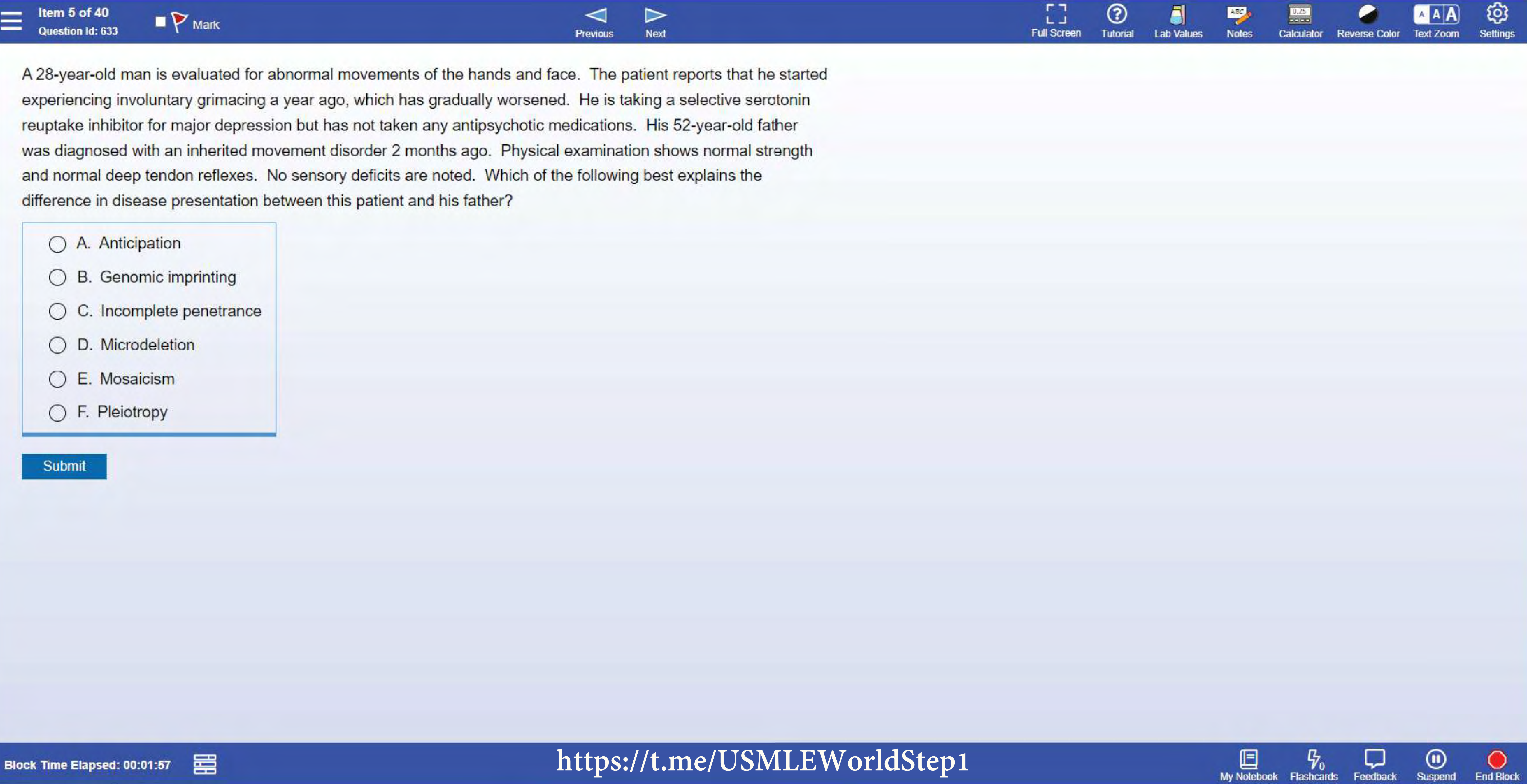
Item 5 of 40
Question Id: 633
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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○ B. Genomic imprinting

○ C. Incomplete penetrance

○ D. Microdeletion

○ E. Mosaicism

○ F. Pleiotropy

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This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive

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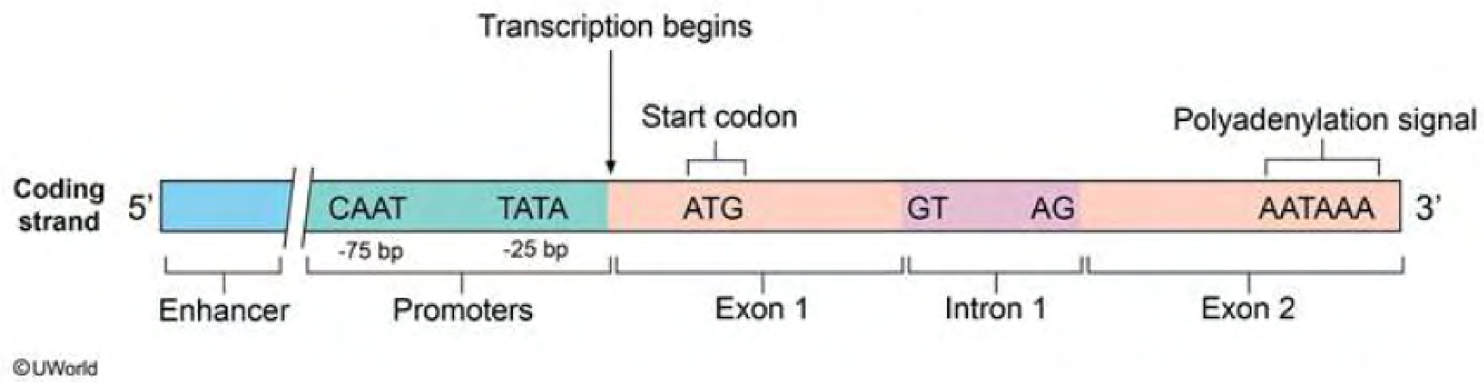
Eukaryotic gene organization


Transcription begins
Start codon
Polyadenylation signal
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Genetics	Genetics (General Principles)	Transcription
Subject	System	Topic

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Item 4 of 40
Question Id: 2025
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive bleeding due to a deficiency in coagulation factor VIII. The disorder can be caused by a variety of different mutations in the factor VIII gene, including deletions in the enhancer sequence.

In eukaryotic gene transcription, nuclear RNA polymerase II uses a DNA template to generate complementary mRNA, which is then processed and translated into protein. Eukaryotic genes have associated promoter and enhancer sequences that mediate transcription. Promoter sequences directly bind general transcription factors and RNA polymerase II upstream from the gene locus, which is necessary for the initiation of transcription **(Choices C and E)**. There are 2 types of eukaryotic promoter regions: the TATA, or Hogness, box, which is located approximately 25 bases upstream from the gene being transcribed; and the CAAT box, which is 70-80 bases upstream from the gene.

In contrast to promoters, **enhancer sequences** bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the **rate of transcription (Choice D)**. Enhancers can be located **upstream or downstream** from the gene being transcribed and may be near the gene or thousands of base pairs away **(Choice B)**. They have also been identified both **within introns** of the gene being transcribed as well as on separate chromosomes. Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

Educational objective:

Enhancers and silencers may be located upstream, downstream, or within a transcribed gene; these gene sequences function to increase and decrease the rate of transcription, respectively. In contrast, promoter regions are typically located 25 or 75 bases upstream from their associated genes and function to initiate transcription.

References

- Regulatory regions in DNA: promoters, enhancers, silencers, and insulators.

Genetics	Genetics (General Principles)	Transcription
Subject	System	Topic

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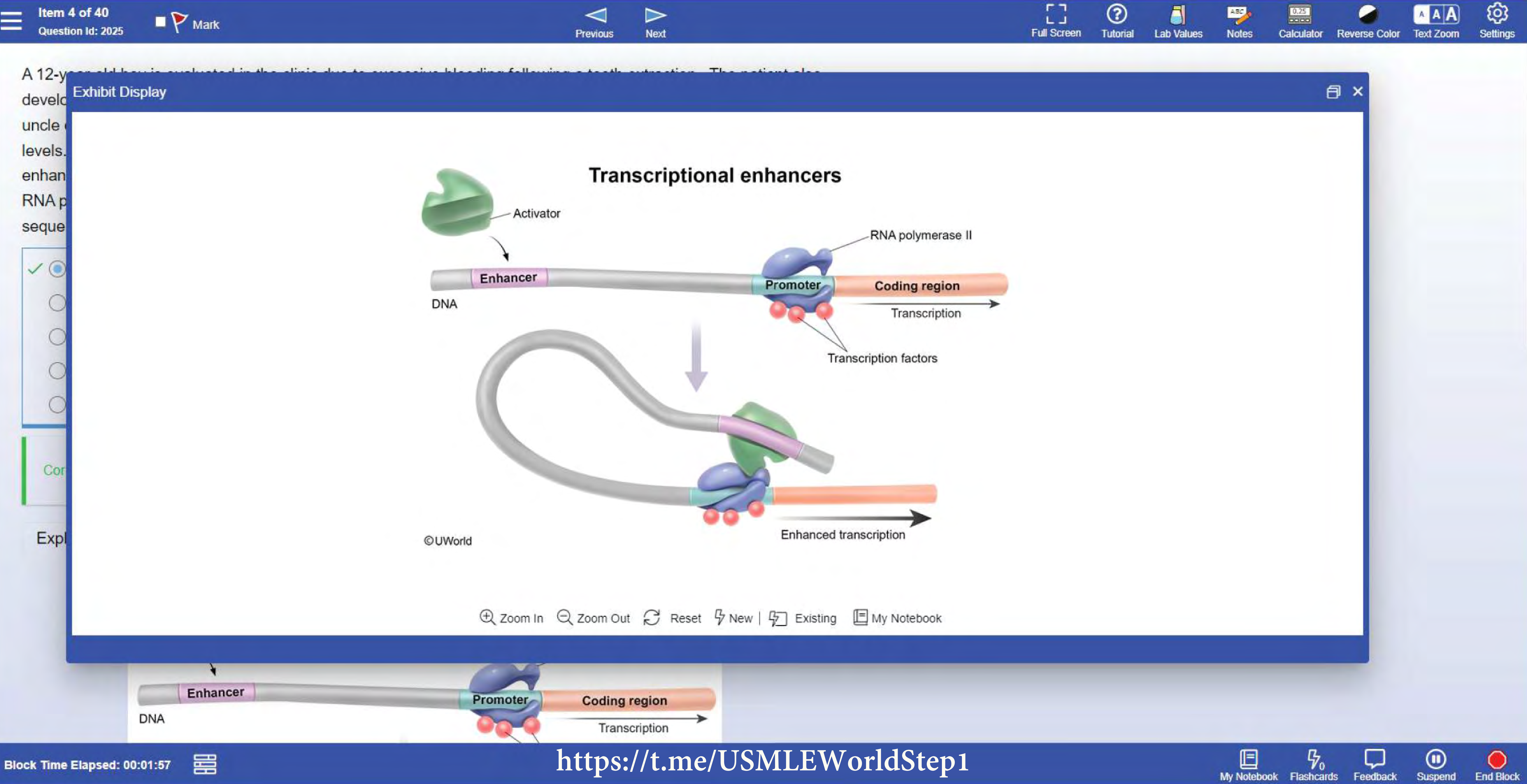
Item 4 of 40
Question Id: 2025
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
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Calculator
Reverse Color
Text Zoom
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Expl

Transcriptional enhancers

Activator
RNA polymerase II
Enhancer
Promoter
Coding region
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Transcription factors
Enhanced transcription
Enhancer
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DNA
Transcription

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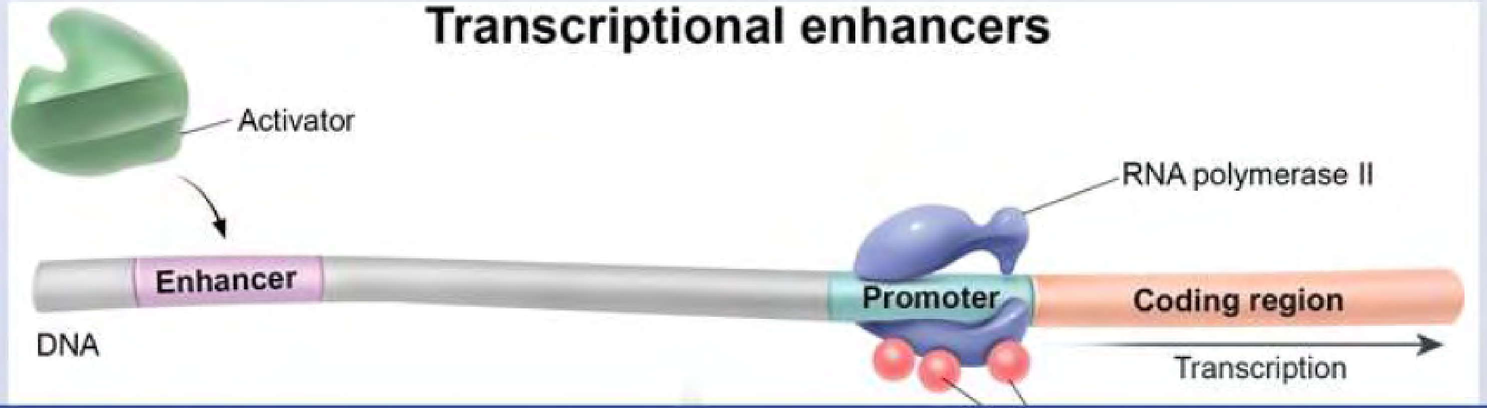
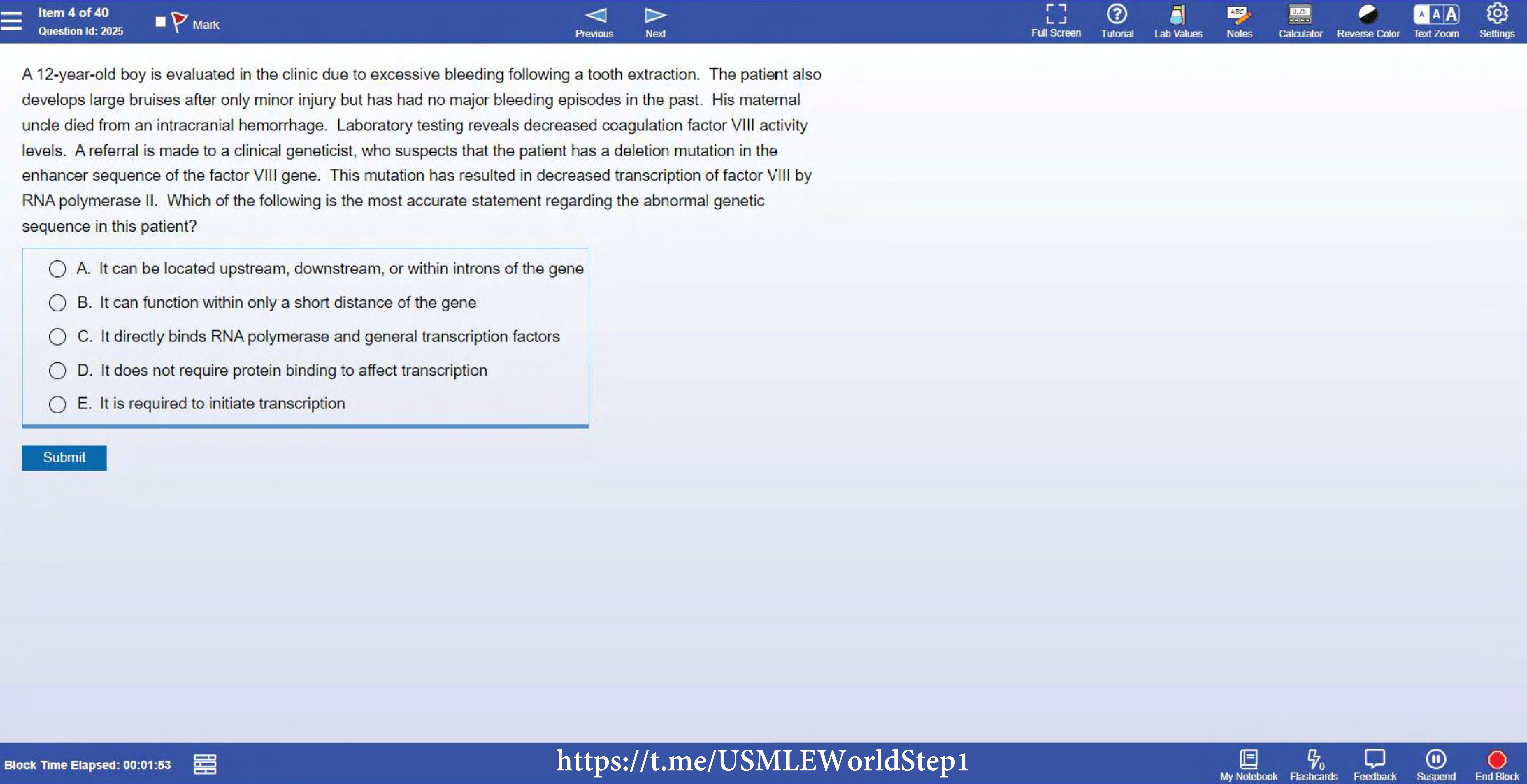
A 12-year-old boy is evaluated in the clinic due to excessive bleeding following a tooth extraction. The patient also develops large bruises after only minor injury but has had no major bleeding episodes in the past. His maternal uncle died from an intracranial hemorrhage. Laboratory testing reveals decreased coagulation factor VIII activity levels. A referral is made to a clinical geneticist, who suspects that the patient has a deletion mutation in the enhancer sequence of the factor VIII gene. This mutation has resulted in decreased transcription of factor VIII by RNA polymerase II. Which of the following is the most accurate statement regarding the abnormal genetic sequence in this patient?

✓ ● A. It can be located upstream, downstream, or within introns of the gene (61%)
○ B. It can function within only a short distance of the gene (7%)
○ C. It directly binds RNA polymerase and general transcription factors (14%)
○ D. It does not require protein binding to affect transcription (4%)
○ E. It is required to initiate transcription (12%)

Correct | 61% Answered correctly | 04 secs Time Spent | 2023 Version

Explanation




Item 4 of 40
Question Id: 2025
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
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○ B. It can function within only a short distance of the gene

○ C. It directly binds RNA polymerase and general transcription factors

○ D. It does not require protein binding to affect transcription

○ E. It is required to initiate transcription

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My Notebook
Flashcards
Feedback
Suspend
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Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 3 of 40
Question Id: 1872

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Cellular adhesion is the means by which one cell binds to another cell, surface, or matrix. The **integrins** are a family of transmembrane protein receptors that interact with the extracellular matrix by binding to specific proteins, including collagen, fibronectin, and laminin. Other adhesion molecule classes include the cadherins, selectins, and Ig superfamily members.

Fibronectins are large glycoproteins produced by fibroblasts and some epithelial cells. Fibronectin binds to integrins, matrix collagen, and glycosaminoglycans, serving as a mediator of cell adhesion and migration. Differential expression of integrin subtypes affects adhesion properties of individual cells, and correlates with **malignant behavior** in a number of tumors, including melanoma.

(Choices A and E) The intracellular domains of the integrins interact with a number of structural proteins, including microfilaments (actin) within the cytoplasm and intermediate filaments (keratin). However, the extracellular domains do not interact with these structures.

(Choices C and D) Hyaluronic acid is a glycosaminoglycan that contributes to water retention in the extracellular matrix, and determines the stiffness of the matrix. Keratan sulfate is a glycosaminoglycan in the extracellular matrix that may play a role in maintaining type I collagen fibril organization in a number of tissues (eg, cornea). However, neither of these is a ligand for integrins.

Educational objective:
Adhesion of cells to the extracellular matrix involves integrin-mediated binding to fibronectin, collagen, and laminin. Differential expression of integrin subtypes affects adhesion properties of individual cells, and has been found to correlate with malignant behavior in a number of tumors.

References

- Integrins: versatile receptors controlling melanocyte adhesion, migration, and proliferation.

Biochemistry	Biochemistry (General Principles)	Cell adhesion molecules
Subject	System	Topic

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irregular border. Excisional biopsy is performed and histopathology reveals malignant melanoma.

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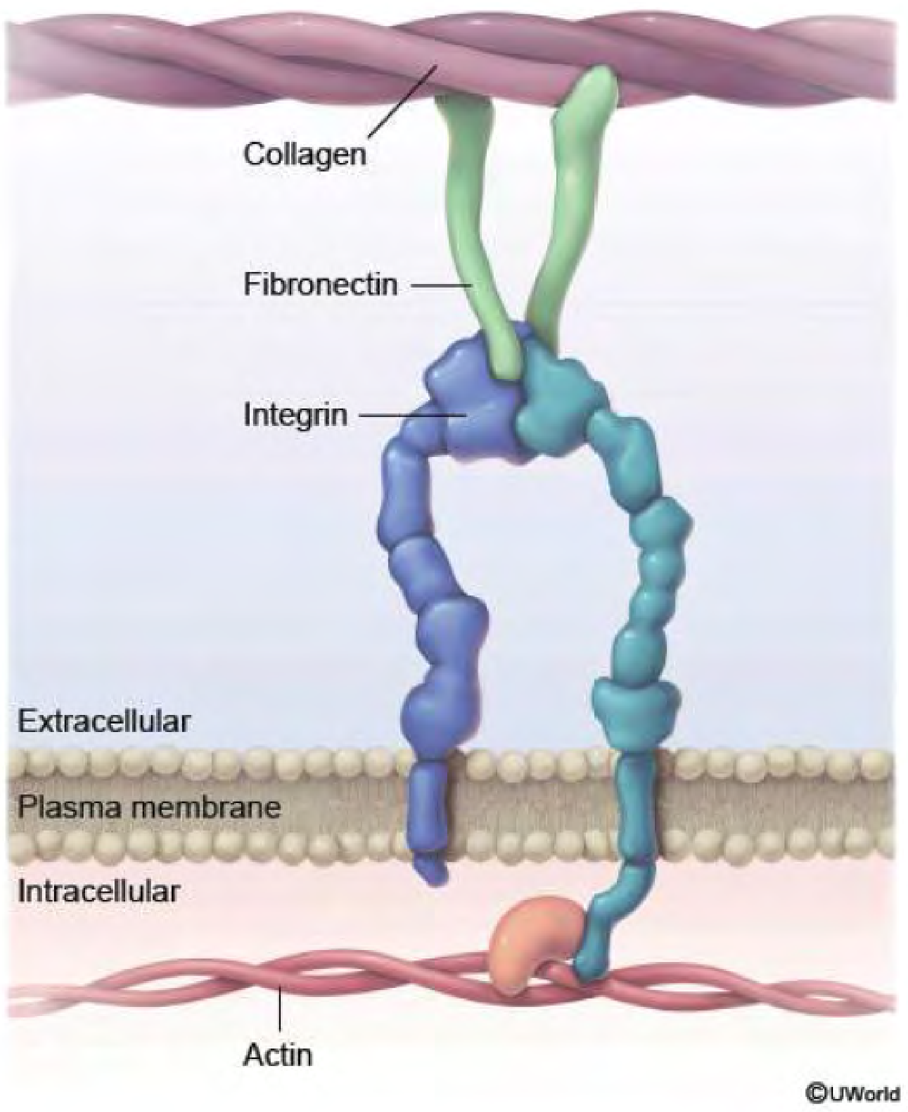
Integrin & fibronectin


Collagen
Fibronectin
Integrin
Extracellular
Plasma membrane
Intracellular
Actin
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Zoom In
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My Notebook

A 68-year-old man comes to the office due to an enlarging mole on his right forearm. The patient is a retired farmer and received a significant amount of sun exposure over the course of his life. On examination, he has a black-brown macular lesion on the dorsum of his right forearm measuring approximately 1 cm in diameter with an irregular border. Excisional biopsy is performed and histopathology reveals malignant melanoma. Immunohistochemical analysis indicates that the malignant cells have decreased integrin expression. These cells are most likely to exhibit poor adhesion to which of the following components of the extracellular matrix?

- ✗ ● A. Actin (12%)
- ✓ ○ B. Fibronectin (48%)
- ○ C. Hyaluronic acid (13%)
- ○ D. Keratan sulfate (9%)
- ○ E. Keratin (15%)

Incorrect
Correct answer
B

48%
Answered correctly

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2023
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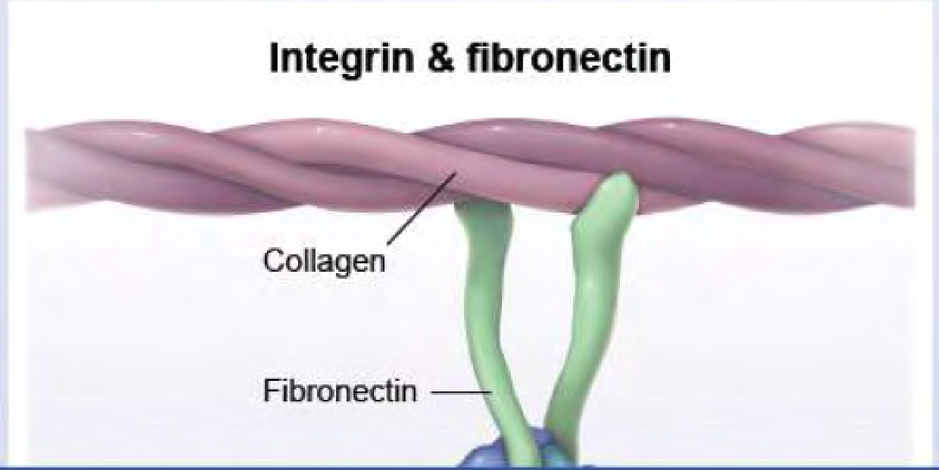
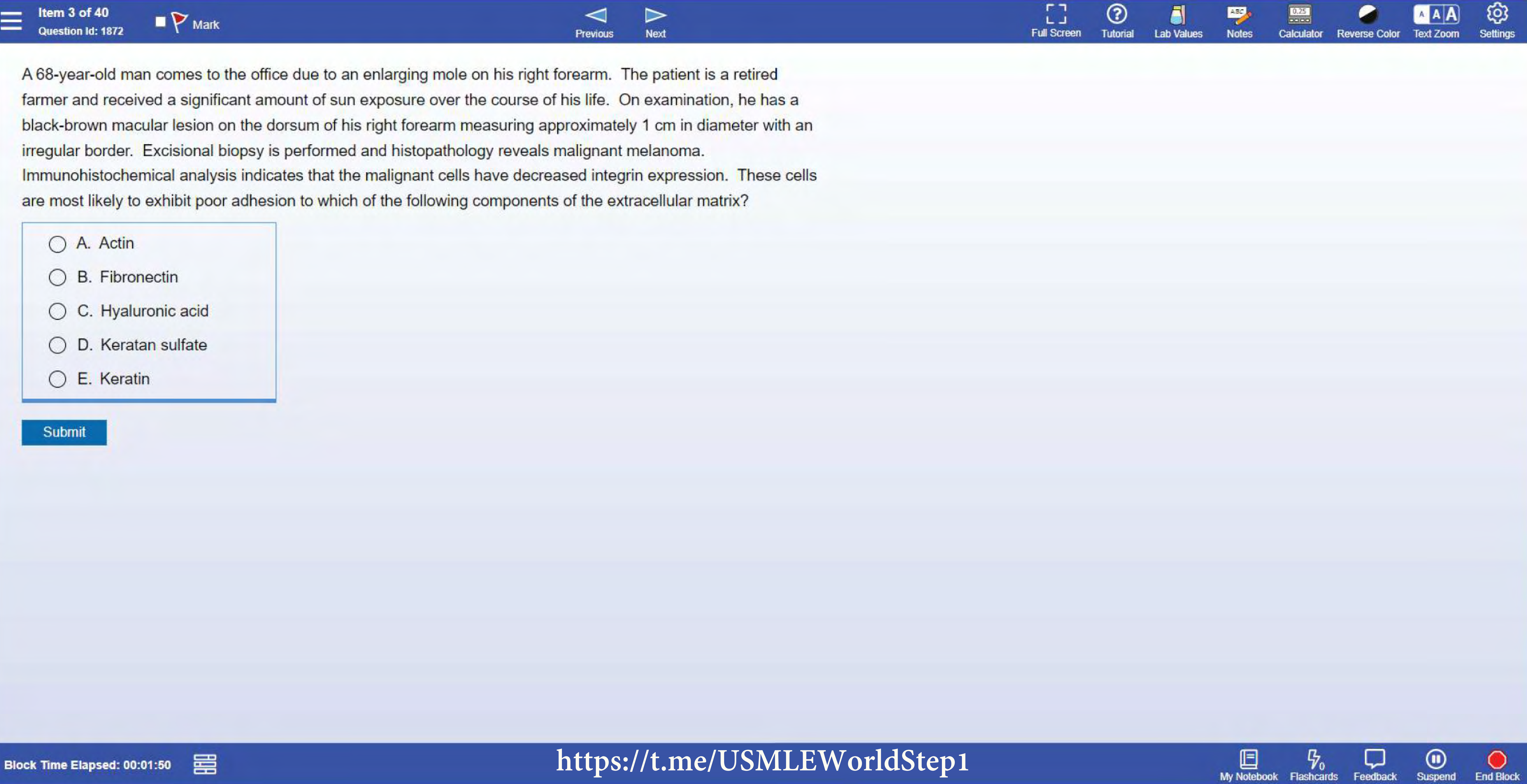
Explanation




Item 3 of 40
Question Id: 1872
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:01:50
My Notebook
Flashcards
Feedback
Suspend
End Block

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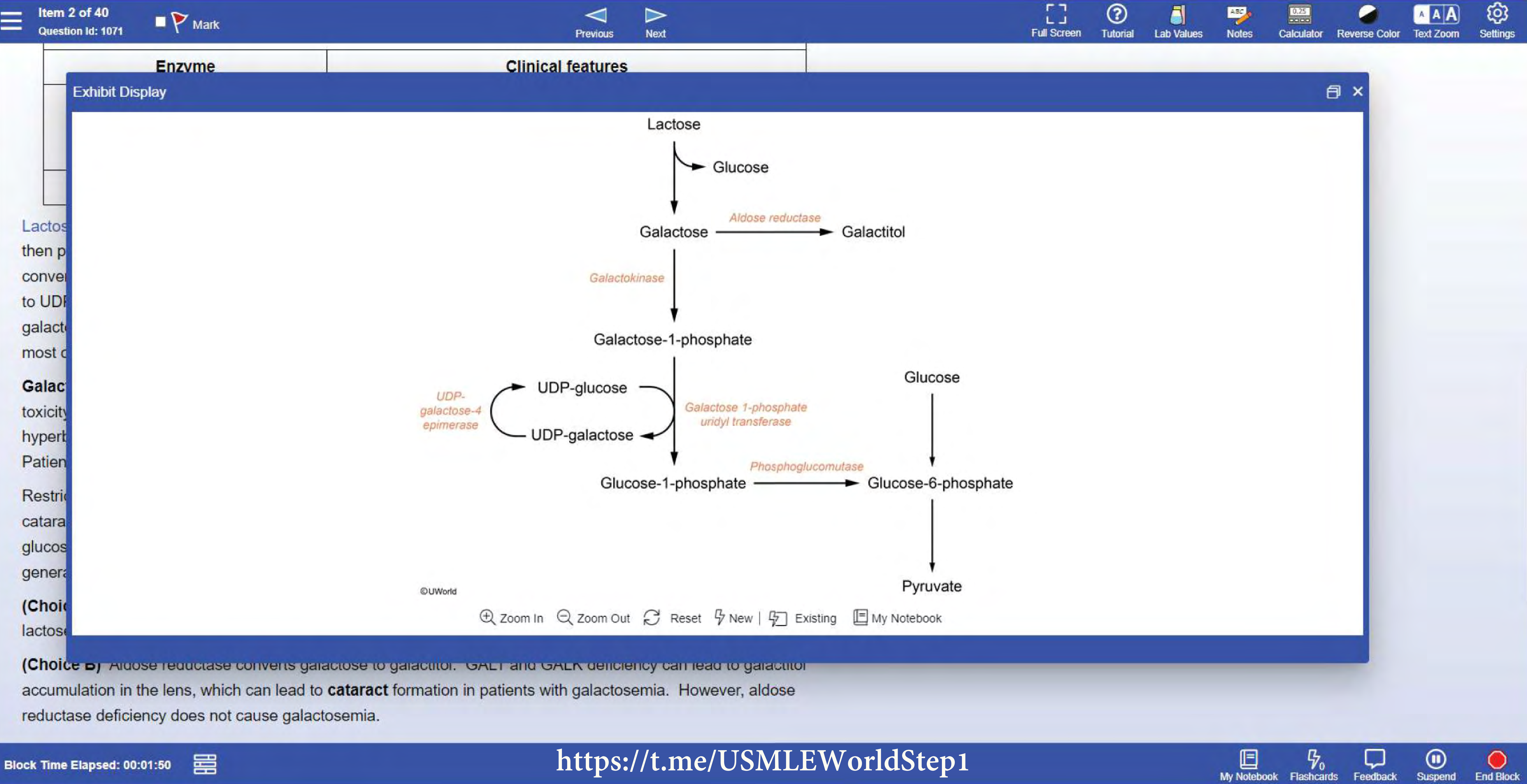
○ B. Fibronectin
○ C. Hyaluronic acid
○ D. Keratan sulfate
○ E. Keratin


Item 2 of 40
Question Id: 1071
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Enzyme	Clinical features

Exhibit Display
Lactose
Glucose
Galactose
Aldose reductase
Galactitol
Galactokinase
Galactose-1-phosphate
UDP-galactose-4 epimerase
UDP-glucose
UDP-galactose
Galactose 1-phosphate uridyl transferase
Glucose
Glucose-1-phosphate
Phosphoglucomutase
Glucose-6-phosphate
Pyruvate
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Galac
toxicity
hyperb
Patien

Restric
catara
glucos
genera

(Choi
lactose

(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol accumulation in the lens, which can lead to **cataract** formation in patients with galactosemia. However, aldose reductase deficiency does not cause galactosemia.

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My Notebook
Flashcards
Feedback
Suspend
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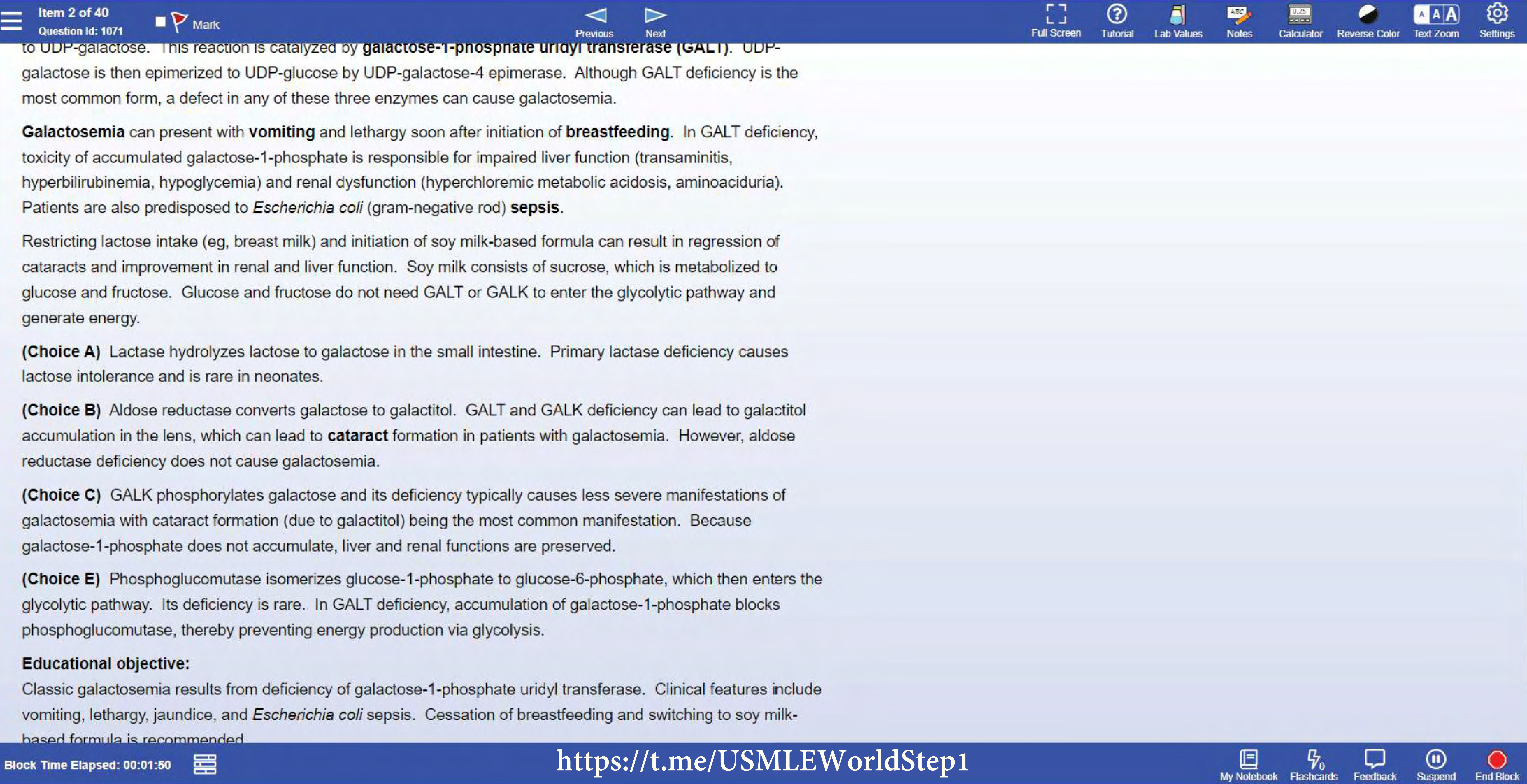


to UDP-galactose. This reaction is catalyzed by **galactose-1-phosphate uridyl transferase (GALT)**. UDP-galactose is then epimerized to UDP-glucose by UDP-galactose-4 epimerase. Although GALT deficiency is the most common form, a defect in any of these three enzymes can cause galactosemia.

Galactosemia can present with **vomiting** and lethargy soon after initiation of **breastfeeding**. In GALT deficiency, toxicity of accumulated galactose-1-phosphate is responsible for impaired liver function (transaminitis, hyperbilirubinemia, hypoglycemia) and renal dysfunction (hyperchloremic metabolic acidosis, aminoaciduria). Patients are also predisposed to *Escherichia coli* (gram-negative rod) **sepsis**.

Restricting lactose intake (eg, breast milk) and initiation of soy milk-based formula can result in regression of cataracts and improvement in renal and liver function. Soy milk consists of sucrose, which is metabolized to glucose and fructose. Glucose and fructose do not need GALT or GALK to enter the glycolytic pathway and generate energy.

(Choice A) Lactase hydrolyzes lactose to galactose in the small intestine. Primary lactase deficiency causes lactose intolerance and is rare in neonates.

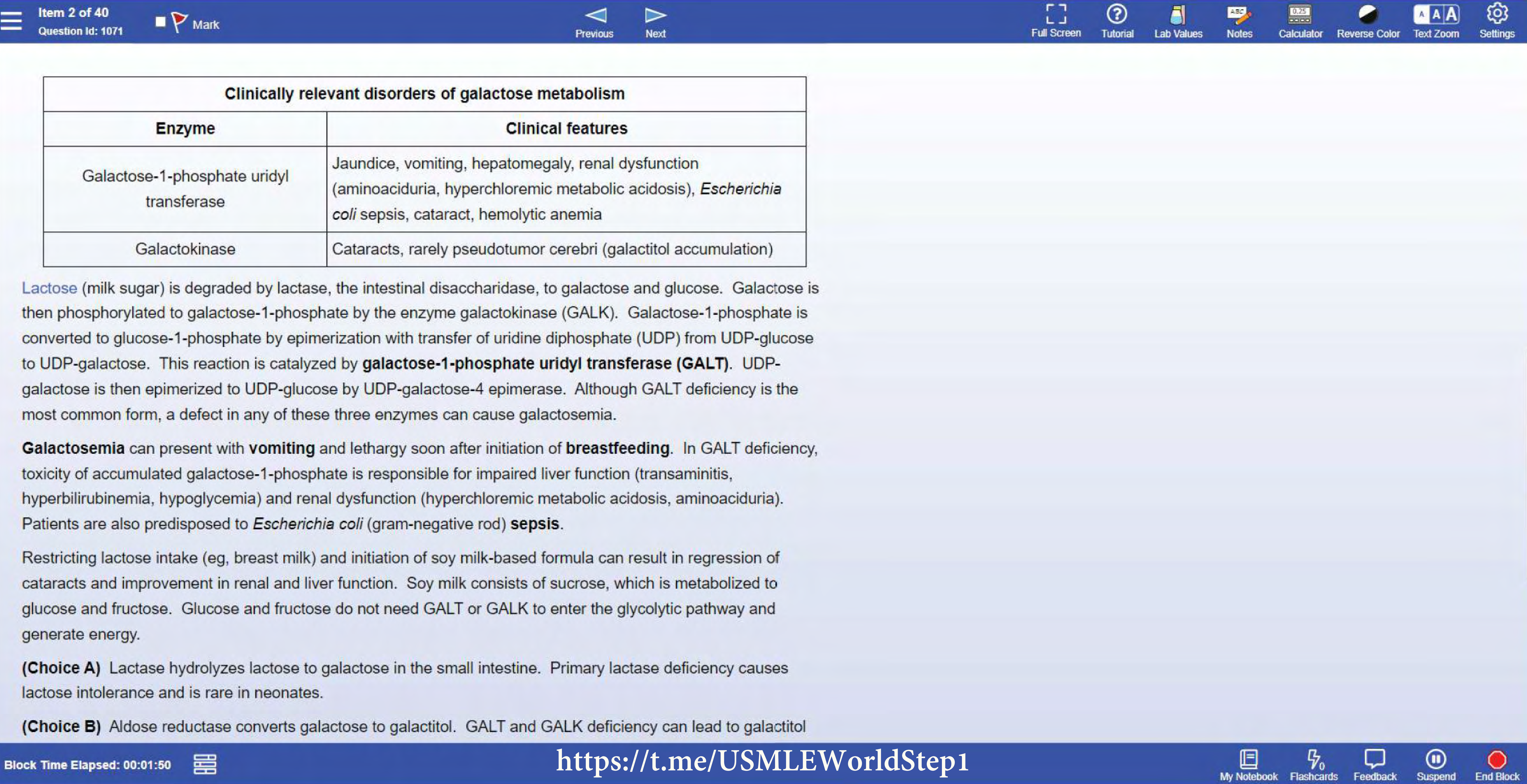
(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol accumulation in the lens, which can lead to **cataract** formation in patients with galactosemia. However, aldose reductase deficiency does not cause galactosemia.

(Choice C) GALK phosphorylates galactose and its deficiency typically causes less severe manifestations of galactosemia with cataract formation (due to galactitol) being the most common manifestation. Because galactose-1-phosphate does not accumulate, liver and renal functions are preserved.

(Choice E) Phosphoglucomutase isomerizes glucose-1-phosphate to glucose-6-phosphate, which then enters the glycolytic pathway. Its deficiency is rare. In GALT deficiency, accumulation of galactose-1-phosphate blocks phosphoglucomutase, thereby preventing energy production via glycolysis.

Educational objective:

Classic galactosemia results from deficiency of galactose-1-phosphate uridyl transferase. Clinical features include vomiting, lethargy, jaundice, and *Escherichia coli* sepsis. Cessation of breastfeeding and switching to soy milk-based formula is recommended.



Clinically relevant disorders of galactose metabolism	
Enzyme	**Clinical features**
Galactose-1-phosphate uridyl transferase	Jaundice, vomiting, hepatomegaly, renal dysfunction (aminoaciduria, hyperchloremic metabolic acidosis), *Escherichia coli* sepsis, cataract, hemolytic anemia
Galactokinase	Cataracts, rarely pseudotumor cerebri (galactitol accumulation)

Lactose (milk sugar) is degraded by lactase, the intestinal disaccharidase, to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme galactokinase (GALK). Galactose-1-phosphate is converted to glucose-1-phosphate by epimerization with transfer of uridine diphosphate (UDP) from UDP-glucose to UDP-galactose. This reaction is catalyzed by **galactose-1-phosphate uridyl transferase (GALT)**. UDP-galactose is then epimerized to UDP-glucose by UDP-galactose-4 epimerase. Although GALT deficiency is the most common form, a defect in any of these three enzymes can cause galactosemia.

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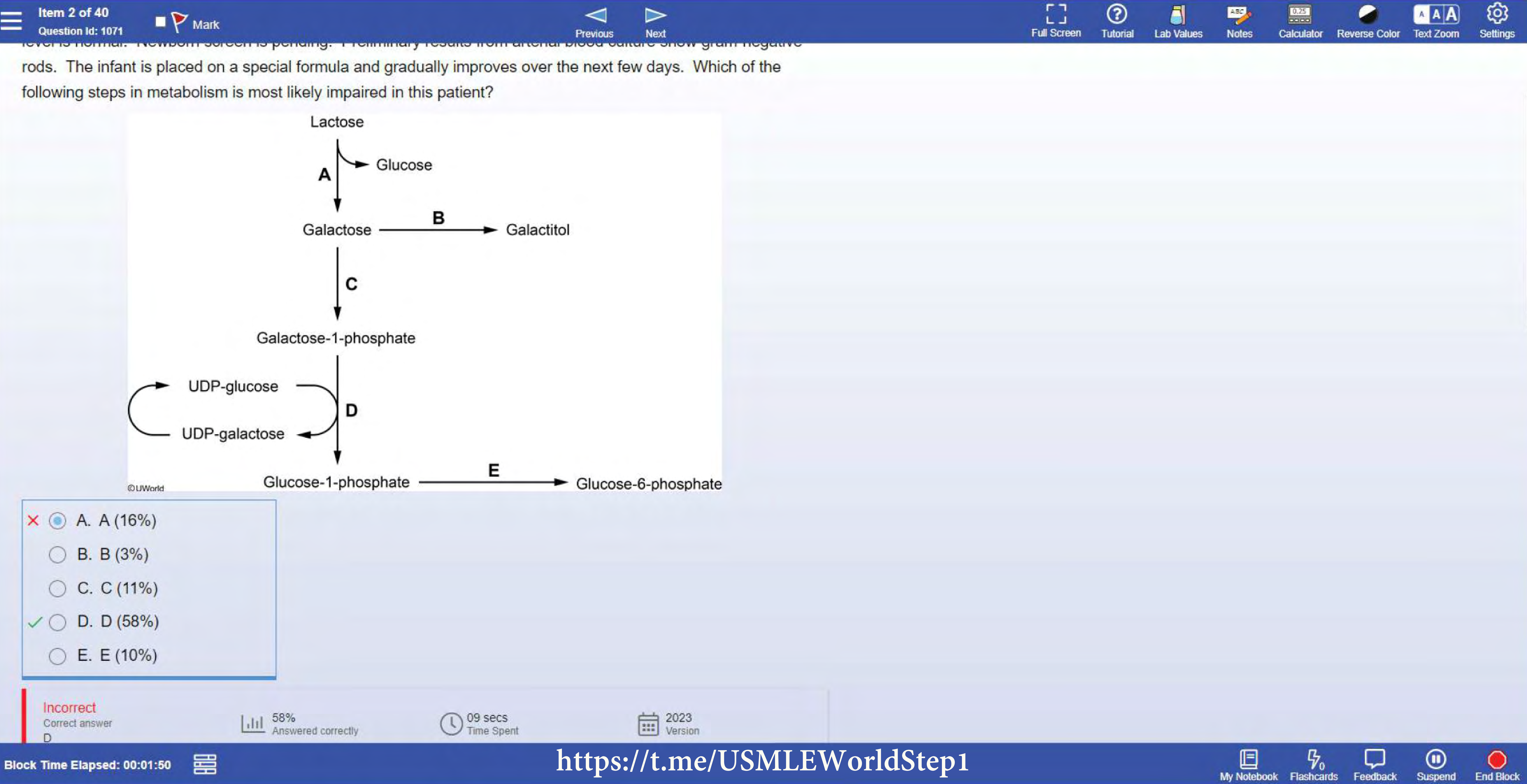
(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol



Item 2 of 40
Question Id: 1071
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

level is normal. Newborn screen is pending. Preliminary results from arterial blood culture show gram-negative rods. The infant is placed on a special formula and gradually improves over the next few days. Which of the following steps in metabolism is most likely impaired in this patient?

Lactose
A
Glucose
Galactose
B
Galactitol
C
Galactose-1-phosphate
UDP-glucose
UDP-galactose
D
Glucose-1-phosphate
E
Glucose-6-phosphate
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✗ ● A. A (16%)

○ B. B (3%)

○ C. C (11%)

✓ ○ D. D (58%)

○ E. E (10%)

Incorrect
Correct answer
D

58%
Answered correctly

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Version

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My Notebook
Flashcards
Feedback
Suspend
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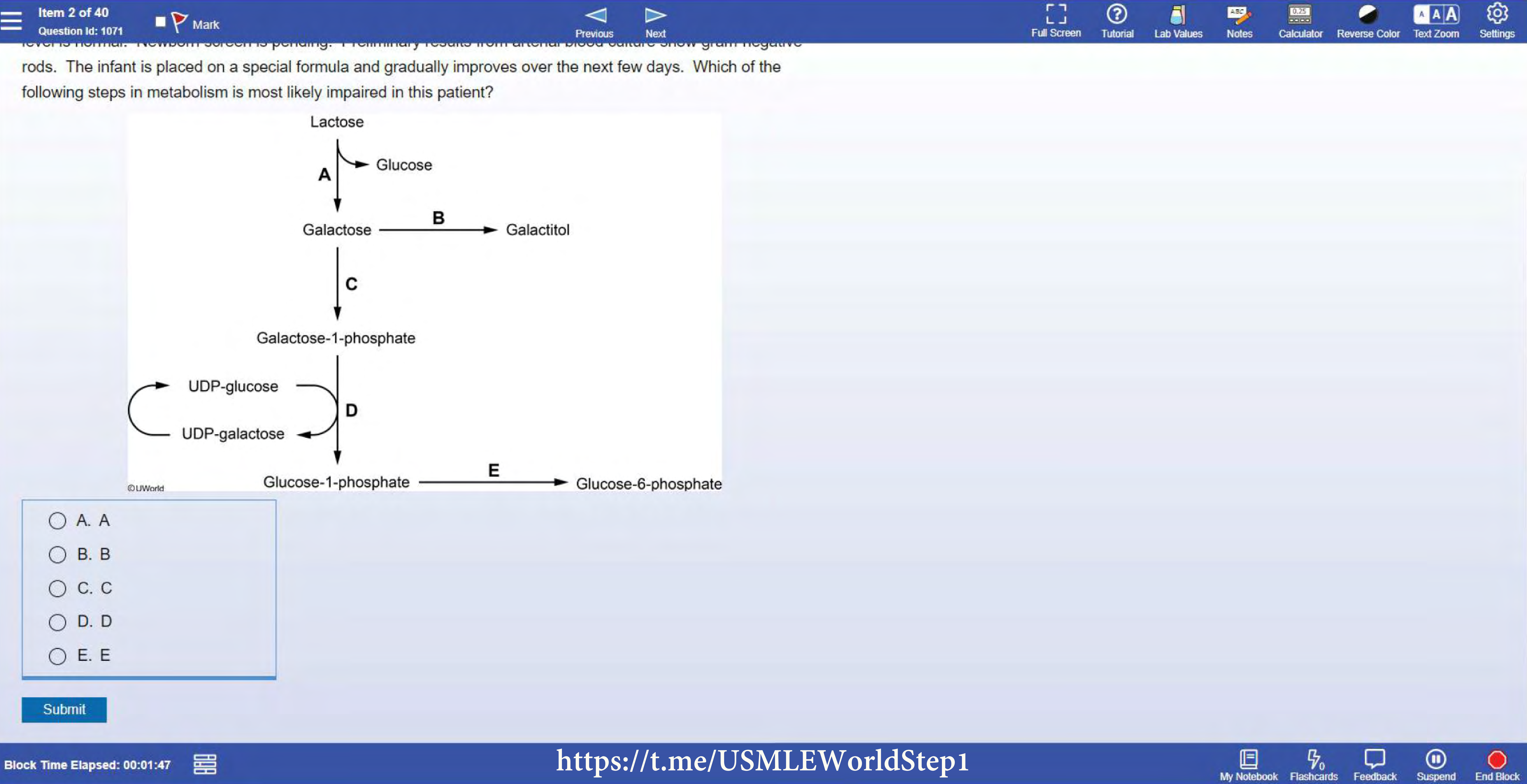
Item 2 of 40
Question Id: 1071
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

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Glucose
A
Galactose
B
Galactitol
C
Galactose-1-phosphate
UDP-glucose
UDP-galactose
D
Glucose-1-phosphate
E
Glucose-6-phosphate
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○ A. A

○ B. B

○ C. C

○ D. D

○ E. E

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Flashcards
Feedback
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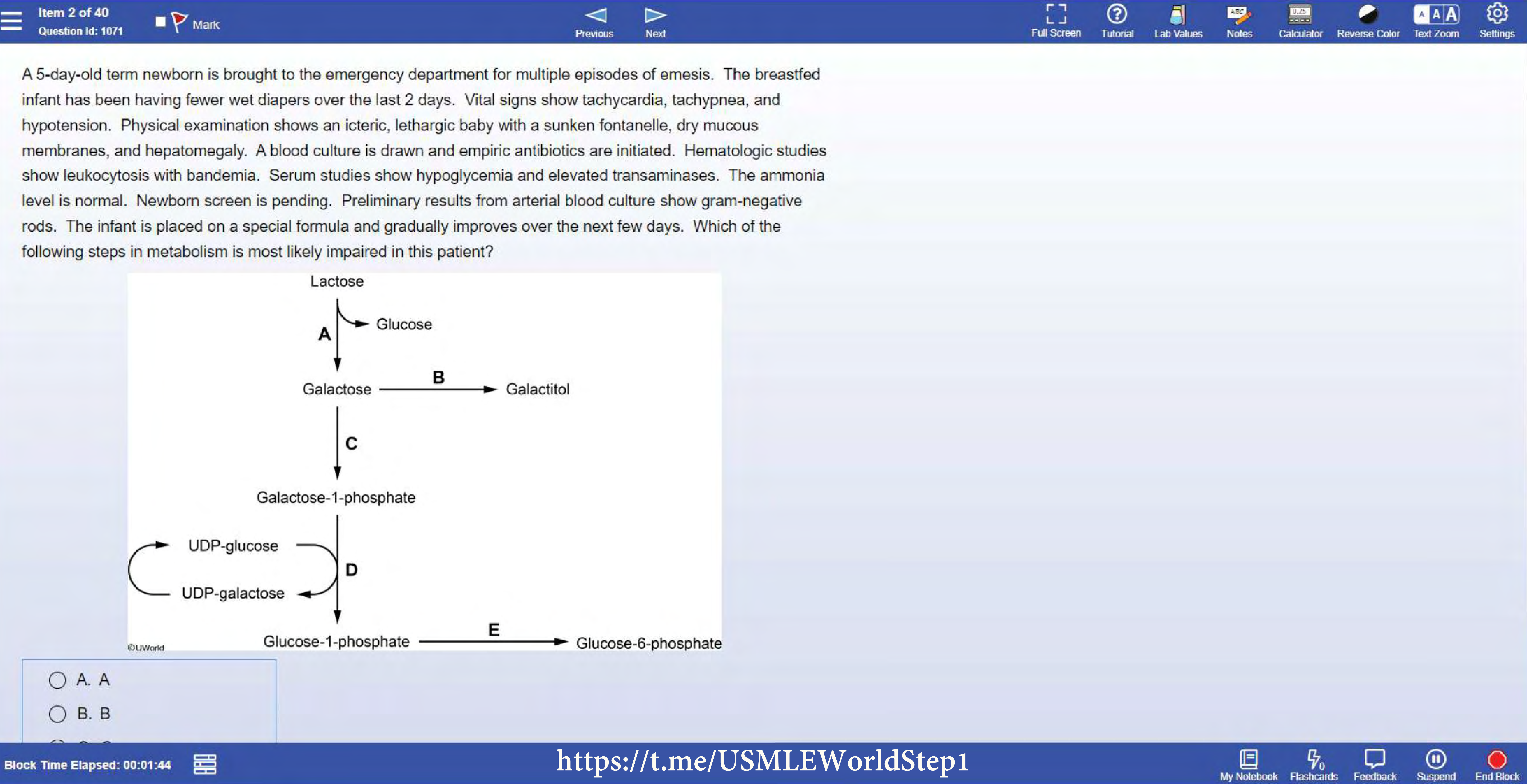
Item 2 of 40
Question Id: 1071
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 5-day-old term newborn is brought to the emergency department for multiple episodes of emesis. The breastfed infant has been having fewer wet diapers over the last 2 days. Vital signs show tachycardia, tachypnea, and hypotension. Physical examination shows an icteric, lethargic baby with a sunken fontanelle, dry mucous membranes, and hepatomegaly. A blood culture is drawn and empiric antibiotics are initiated. Hematologic studies show leukocytosis with bandemia. Serum studies show hypoglycemia and elevated transaminases. The ammonia level is normal. Newborn screen is pending. Preliminary results from arterial blood culture show gram-negative rods. The infant is placed on a special formula and gradually improves over the next few days. Which of the following steps in metabolism is most likely impaired in this patient?

Lactose
A
Glucose
Galactose
B
Galactitol
C
Galactose-1-phosphate
UDP-glucose
UDP-galactose
D
Glucose-1-phosphate
E
Glucose-6-phosphate
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○ A. A
○ B. B

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My Notebook
Flashcards
Feedback
Suspend
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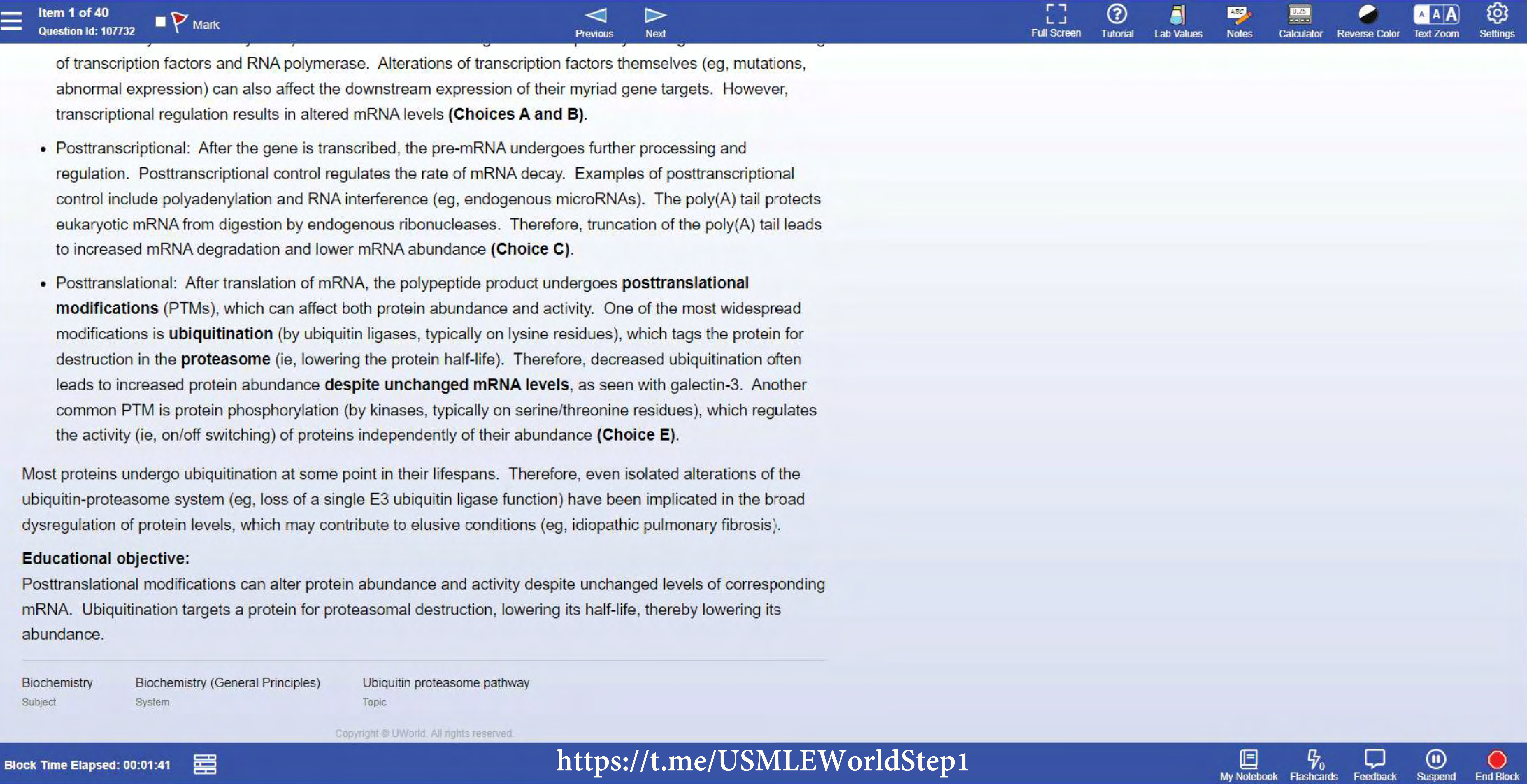

of transcription factors and RNA polymerase. Alterations of transcription factors themselves (eg, mutations, abnormal expression) can also affect the downstream expression of their myriad gene targets. However, transcriptional regulation results in altered mRNA levels **(Choices A and B)**.

- Posttranscriptional: After the gene is transcribed, the pre-mRNA undergoes further processing and regulation. Posttranscriptional control regulates the rate of mRNA decay. Examples of posttranscriptional control include polyadenylation and RNA interference (eg, endogenous microRNAs). The poly(A) tail protects eukaryotic mRNA from digestion by endogenous ribonucleases. Therefore, truncation of the poly(A) tail leads to increased mRNA degradation and lower mRNA abundance **(Choice C)**.
- Posttranslational: After translation of mRNA, the polypeptide product undergoes **posttranslational modifications** (PTMs), which can affect both protein abundance and activity. One of the most widespread modifications is **ubiquitination** (by ubiquitin ligases, typically on lysine residues), which tags the protein for destruction in the **proteasome** (ie, lowering the protein half-life). Therefore, decreased ubiquitination often leads to increased protein abundance **despite unchanged mRNA levels**, as seen with galectin-3. Another common PTM is protein phosphorylation (by kinases, typically on serine/threonine residues), which regulates the activity (ie, on/off switching) of proteins independently of their abundance **(Choice E)**.

Most proteins undergo ubiquitination at some point in their lifespans. Therefore, even isolated alterations of the ubiquitin-proteasome system (eg, loss of a single E3 ubiquitin ligase function) have been implicated in the broad dysregulation of protein levels, which may contribute to elusive conditions (eg, idiopathic pulmonary fibrosis).

Educational objective:

Posttranslational modifications can alter protein abundance and activity despite unchanged levels of corresponding mRNA. Ubiquitination targets a protein for proteasomal destruction, lowering its half-life, thereby lowering its abundance.

Biochemistry	Biochemistry (General Principles)	Ubiquitin proteasome pathway
Subject	System	Topic

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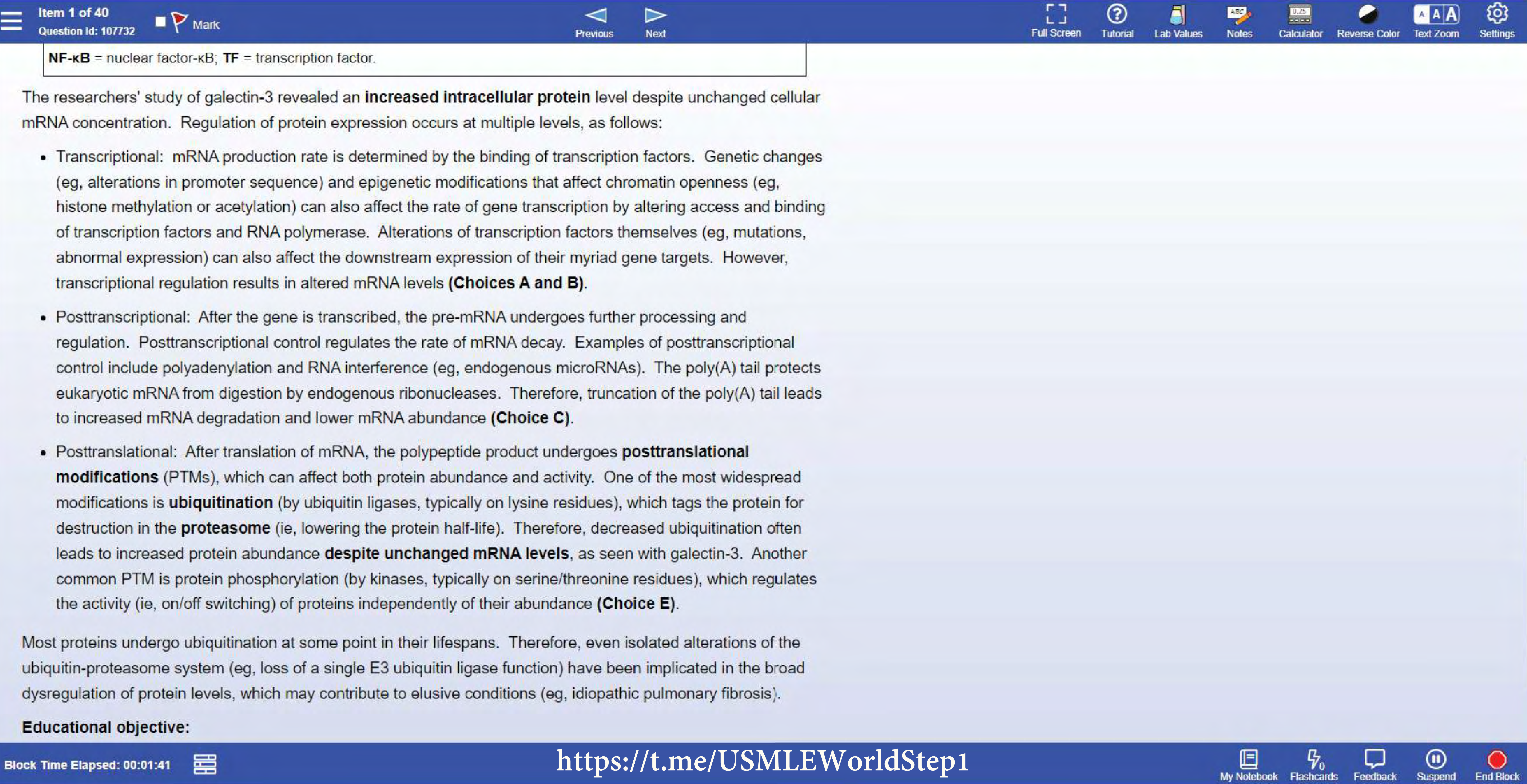

NF-κB = nuclear factor-κB; **TF** = transcription factor.

The researchers' study of galectin-3 revealed an **increased intracellular protein** level despite unchanged cellular mRNA concentration. Regulation of protein expression occurs at multiple levels, as follows:

- Transcriptional: mRNA production rate is determined by the binding of transcription factors. Genetic changes (eg, alterations in promoter sequence) and epigenetic modifications that affect chromatin openness (eg, histone methylation or acetylation) can also affect the rate of gene transcription by altering access and binding of transcription factors and RNA polymerase. Alterations of transcription factors themselves (eg, mutations, abnormal expression) can also affect the downstream expression of their myriad gene targets. However, transcriptional regulation results in altered mRNA levels **(Choices A and B)**.
- Posttranscriptional: After the gene is transcribed, the pre-mRNA undergoes further processing and regulation. Posttranscriptional control regulates the rate of mRNA decay. Examples of posttranscriptional control include polyadenylation and RNA interference (eg, endogenous microRNAs). The poly(A) tail protects eukaryotic mRNA from digestion by endogenous ribonucleases. Therefore, truncation of the poly(A) tail leads to increased mRNA degradation and lower mRNA abundance **(Choice C)**.
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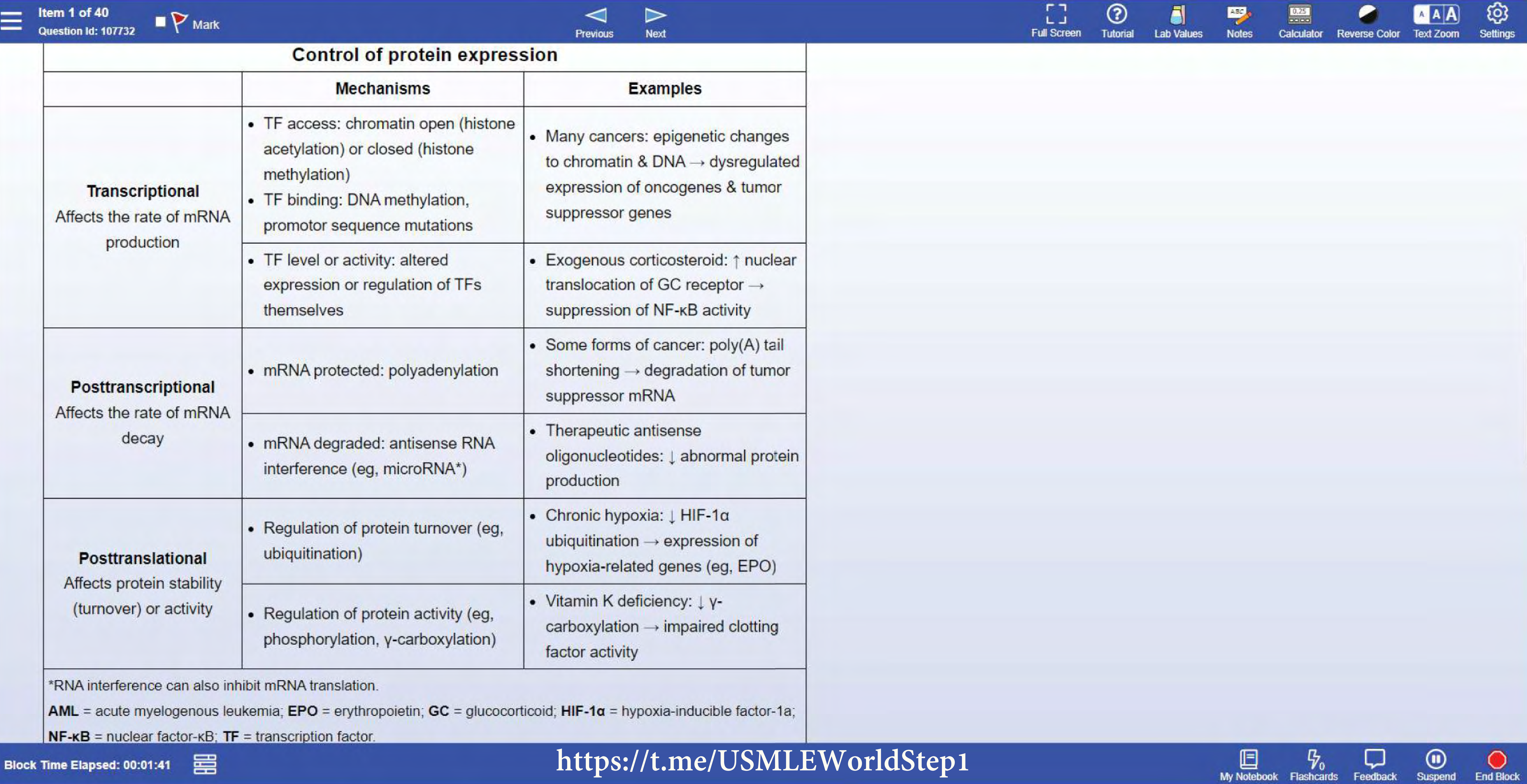
Most proteins undergo ubiquitination at some point in their lifespans. Therefore, even isolated alterations of the ubiquitin-proteasome system (eg, loss of a single E3 ubiquitin ligase function) have been implicated in the broad dysregulation of protein levels, which may contribute to elusive conditions (eg, idiopathic pulmonary fibrosis).

Educational objective:

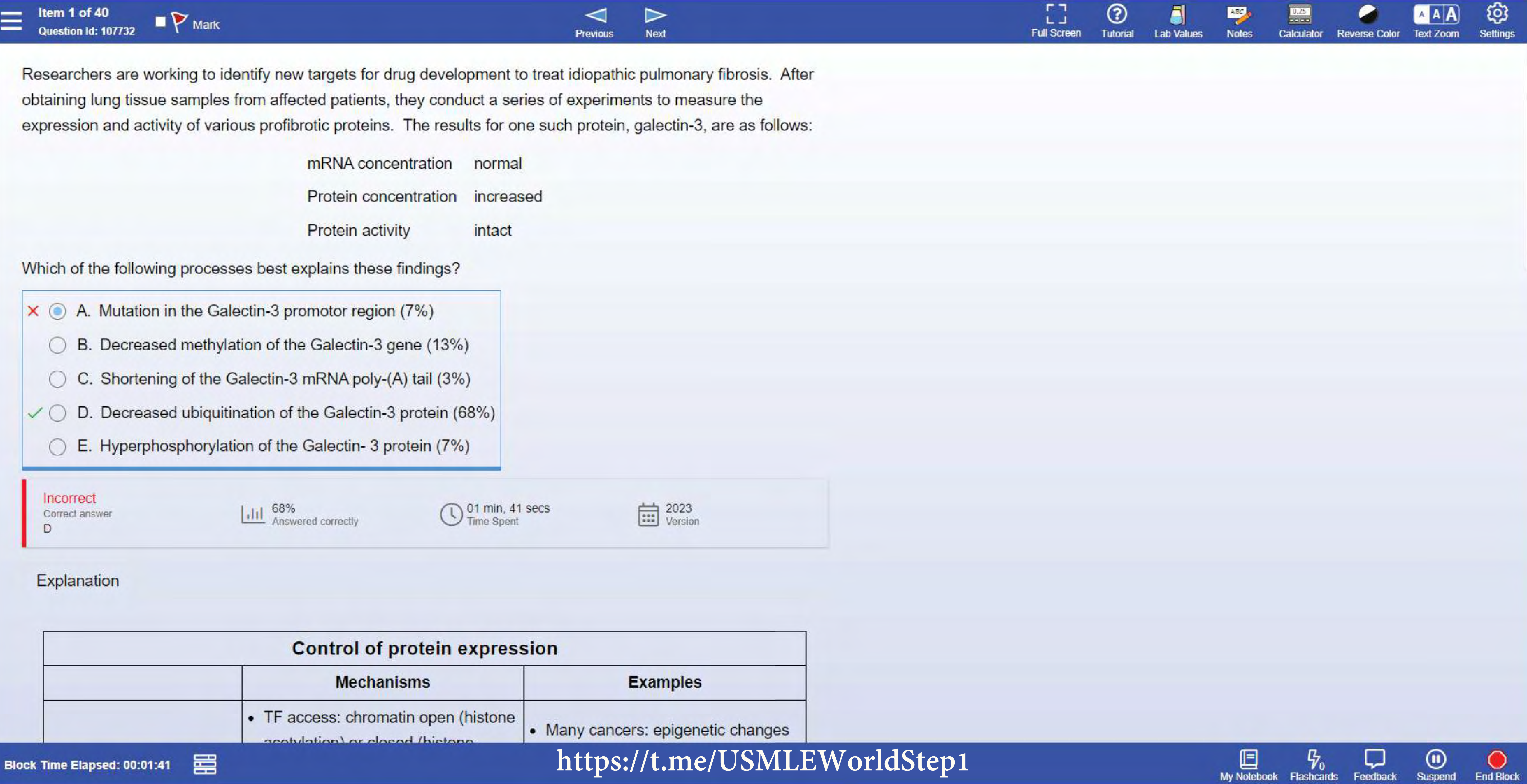

Item 1 of 40
Question Id: 107732
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:01:41
My Notebook
Flashcards
Feedback
Suspend
End Block

Control of protein expression

	Mechanisms	Examples
Transcriptional Affects the rate of mRNA production	• TF access: chromatin open (histone acetylation) or closed (histone methylation) • TF binding: DNA methylation, promotor sequence mutations	• Many cancers: epigenetic changes to chromatin & DNA → dysregulated expression of oncogenes & tumor suppressor genes
	• TF level or activity: altered expression or regulation of TFs themselves	• Exogenous corticosteroid: ↑ nuclear translocation of GC receptor → suppression of NF-κB activity
Posttranscriptional Affects the rate of mRNA decay	• mRNA protected: polyadenylation	• Some forms of cancer: poly(A) tail shortening → degradation of tumor suppressor mRNA
	• mRNA degraded: antisense RNA interference (eg, microRNA*)	• Therapeutic antisense oligonucleotides: ↓ abnormal protein production
Posttranslational Affects protein stability (turnover) or activity	• Regulation of protein turnover (eg, ubiquitination)	• Chronic hypoxia: ↓ HIF-1α ubiquitination → expression of hypoxia-related genes (eg, EPO)
	• Regulation of protein activity (eg, phosphorylation, γ-carboxylation)	• Vitamin K deficiency: ↓ γ-carboxylation → impaired clotting factor activity

*RNA interference can also inhibit mRNA translation.

AML = acute myelogenous leukemia; **EPO** = erythropoietin; **GC** = glucocorticoid; **HIF-1α** = hypoxia-inducible factor-1a; **NF-κB** = nuclear factor-κB; **TF** = transcription factor.


Item 1 of 40
Question Id: 107732
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Researchers are working to identify new targets for drug development to treat idiopathic pulmonary fibrosis. After obtaining lung tissue samples from affected patients, they conduct a series of experiments to measure the expression and activity of various profibrotic proteins. The results for one such protein, galectin-3, are as follows:

mRNA concentration	normal
Protein concentration	increased
Protein activity	intact

Which of the following processes best explains these findings?

✗ ● A. Mutation in the Galectin-3 promotor region (7%)
○ B. Decreased methylation of the Galectin-3 gene (13%)
○ C. Shortening of the Galectin-3 mRNA poly-(A) tail (3%)
✓ ○ D. Decreased ubiquitination of the Galectin-3 protein (68%)
○ E. Hyperphosphorylation of the Galectin- 3 protein (7%)

Incorrect
Correct answer
D

68%
Answered correctly

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Explanation

Control of protein expression		
	Mechanisms	**Examples**
	• TF access: chromatin open (histone acetylation) or closed (histone	• Many cancers: epigenetic changes

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My Notebook
Flashcards
Feedback
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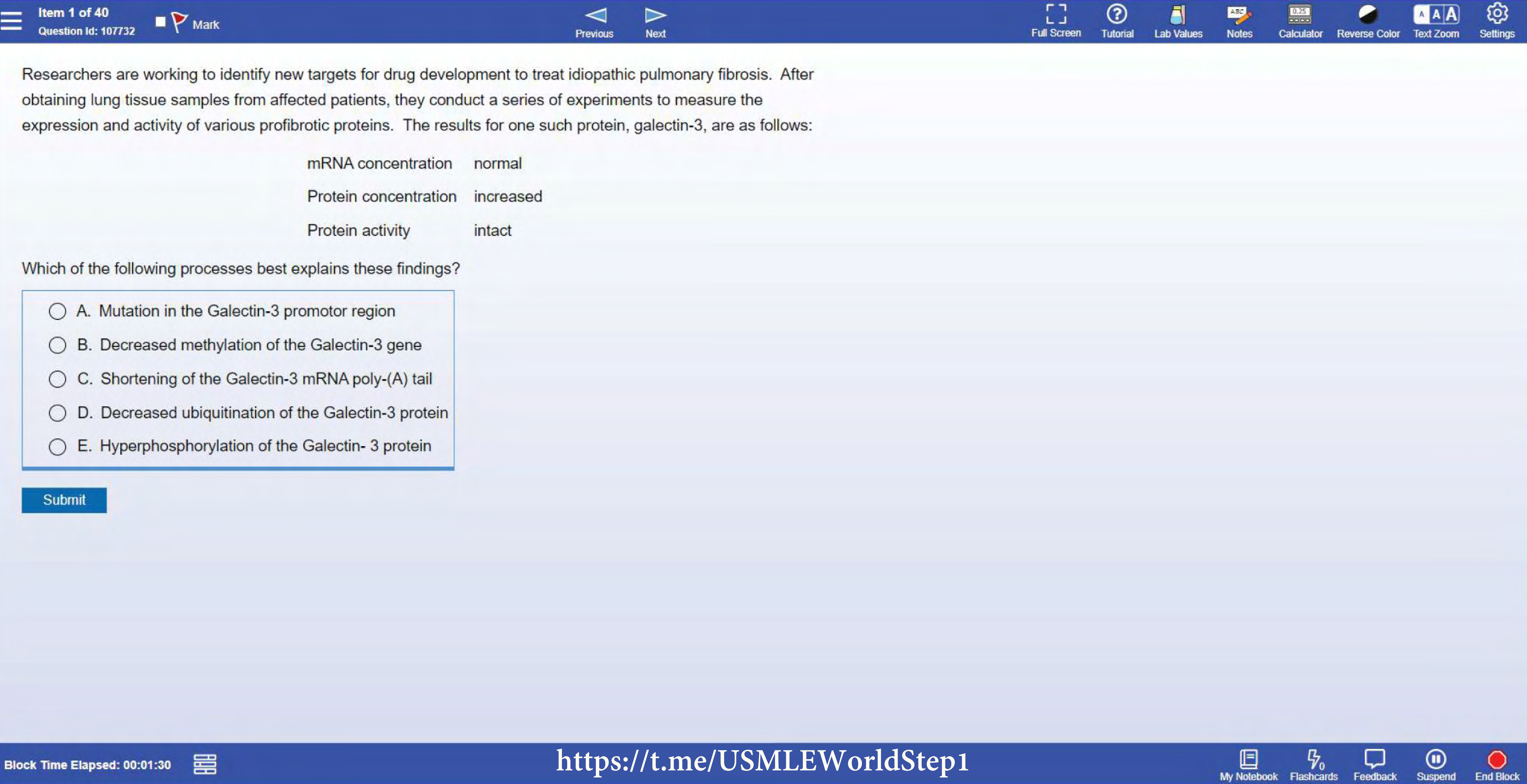
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Next
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Tutorial
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My Notebook
Flashcards
Feedback
Suspend
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